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WITH

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VOLUME 106 • NUMBER 6

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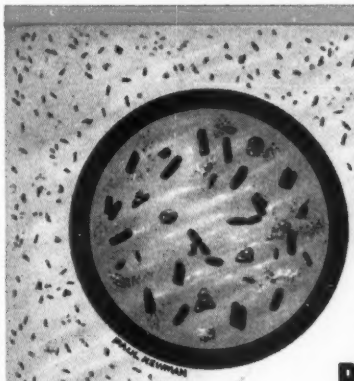

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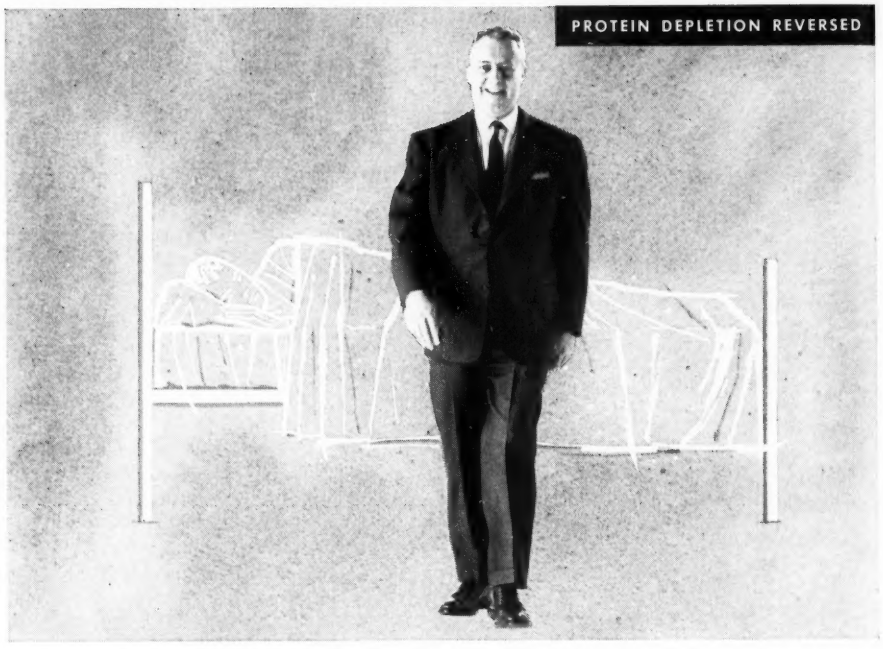

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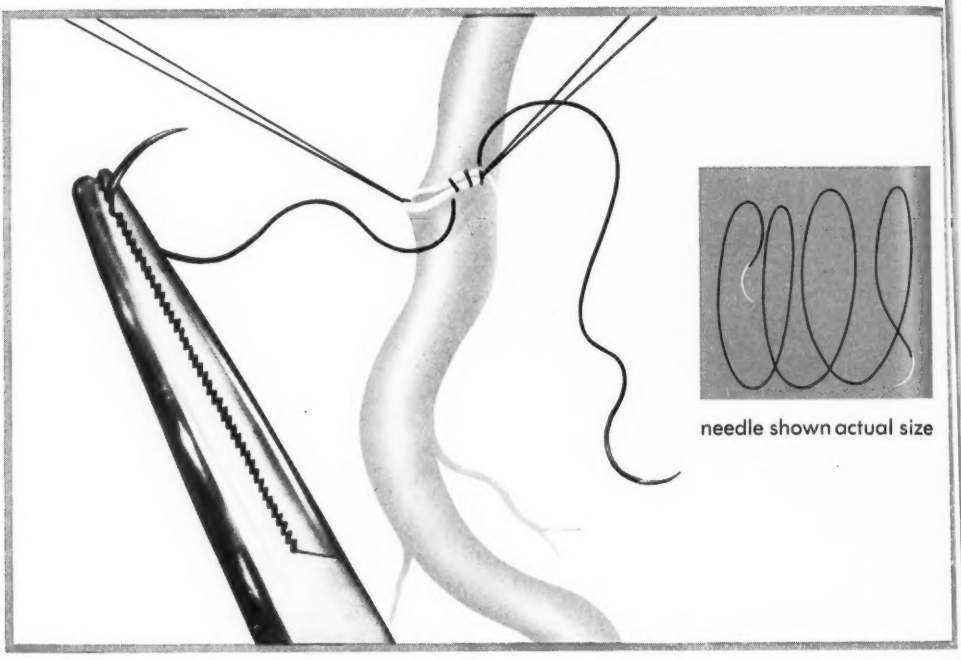

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VOLUME 106
NUMBER 6

CONTENTS

LYMPHOID POLYPS (BENIGN LYMPHOMA) OF THE RECTUM AND ANUS. *Fred Holtz, M.D.*, and *Lewis A. Schmidt, III, M.D.*, Ann Arbor, Michigan 639

FAILURE OF MIGRATION OF THE RECTAL OPENING AS THE CAUSE FOR MOST CASES OF IMPERFORATE ANUS. *Alexander H. Bill, Jr., M.D.*, Seattle, Washington, and *Robert J. Johnson, M.D.*, Morgantown, West Virginia 643

MULTICENTRIC CARCINOMAS OF THE ORAL CAVITY. *Charles G. Moertel, M.D.*, and *Edward L. Foss, M.D.*, Rochester, Minnesota 652

LESIONS OF THE SALIVARY GLANDS. *D. G. McEachen, M.D., D. F. Moore, M.D., B.Sc., F.R.C.P.(C), E. M. Nanson, M.B., Ch.B.(N.Z.), F.R.C.S., F.A.C.S.*, and *T. A. Watson, M.B., Ch.B.(N.Z.), D.M.R.*, Saskatoon, Saskatchewan, Canada 655

A COMPARISON OF IN VIVO CHANGES FOLLOWING ADMINISTRATION OF STRANGULATION OBSTRUCTION FLUID AND CLOSTRIDIUM WELCHII TOXIN. *William O. Barnett, M.D., F.A.C.S.*, and *William A. Neely, M.D.*, Jackson, Mississippi 667

THE PATTERN OF WOUND HEALING OF SKIN AUTOGRAFTS AND SKIN HOMOGRAFTS IN THE RAT. *J. M. Arguedas, M.D.*, and *R. Pérez-Tamayo, M.D.*, México, Distrito Federal. 671

THE SURGICAL TREATMENT OF AORTIC INSUFFICIENCY BY OPEN PLASTIC REVISION OF THE TRICUSPID AORTIC VALVE TO A BICUSPID VALVE. *Joseph J. Garamella, M.D., Ph.D., James G. Andersen, M.D.*, and *Reuben Oropeza, M.D.*, Minneapolis, Minnesota ... 679

THE PAPILLA OF VATER AND DISTAL PORTIONS OF THE COMMON BILE DUCT AND DUCT OF WIRSUNG. *Herbert F. Newman, M.D., Sidney B. Weinberg, M.D., Ernest B. Newman, M.D.*, and *Jane D. Northup, M.D.*, New York, New York 687

FIVE YEAR SURVIVAL AFTER ANTERIOR RESECTION FOR CARCINOMA OF THE RECTUM AND RECTOSIGMOID. *Charles W. Mayo, M.D., F.A.C.S., Martin Y. Laberge, M.D.*, and *William M. Hardy, M.D.*, Rochester, Minnesota 695

[CONTENTS CONTINUED ON PAGE 7]

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A STUDY OF THE EFFECTIVENESS OF "HIGH PRESSURE" CARDIOPNEUMONOPEXY IN MYOCARDIAL REVASCULARIZATION. *John F. Prudden, M.D., F.A.C.S.*, New York, New York 702

EXPERIMENTAL IMPLANTATION OF ARTERIAL HOMOGRAFTS INTO THE VENTRICULAR MYOCARDIUM. *David C. Sabiston, Jr., M.D., F.A.C.S.*, and *Eric W. Fonkalsrud, M.D.*, Baltimore, Maryland 709

AUSCULTATION AS AN IMPORTANT AID TO THE DIAGNOSIS OF FRACTURES. *John C. Colwill, M.D.*, and *Elliot H. Berg, M.D.*, Brooklyn, New York 713

THE GLANDULAR STRUCTURES OF THE CERVIX UTERI. *C. Frederic Fluhmann, M.D.*, San Francisco, California 715

SIMPLE EXCISION OF THE UNATTACHED LAMINA FOR SPONDYLOLYSIS. *Edwin M. Todd, Jr., M.D.*, Long Beach, California, and *W. James Gardner, M.D., F.A.C.S.*, Cleveland, Ohio 724

LYMPH FOLLICLES IN THE CERVIX UTERI. *N. J. Demetrakopoulos, M.D.*, and *R. R. Greene, M.D.*, Chicago, Illinois 729

PREOPERATIVE MANAGEMENT OF BLOOD LOSS ANEMIA. *Ernest Beutler, M.D.*, Chicago . 734

EDITORIALS

SPECIALIZATION VERSUS GENERALIZATION, THE DILEMMA OF SURGICAL TRAINING. *George Crile, Jr., M.D., F.A.C.S.*, Cleveland, Ohio 739

BEHOLD, THE TORCH! *R. Morton Bolman, M.D., F.A.C.S.*, Fort Wayne, Indiana 741

THE SURGEON AT WORK

THE TECHNIQUE OF ANASTOMOSING SMALL ARTERIES. *Bernard Seidenberg, M.D., Elliott S. Hurwitt, M.D., F.A.C.S.*, and *Charles A. Carton, M.D., F.A.C.S.*, New York, New York 743

TELEVISION RADIOSCOPY DURING OPERATIONS ON THE BILIARY PASSAGES. *P. Mallet-Guy, M.D., F.A.C.S.(Hon.)*, Lyon, France 747

[CONTENTS CONTINUED ON PAGE 9]

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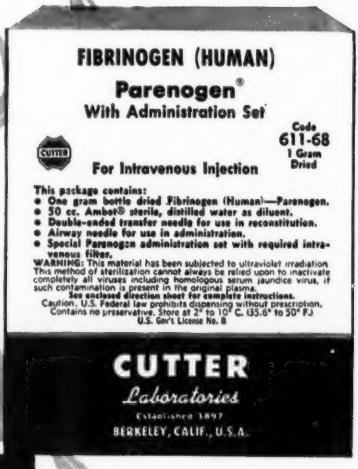
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A Technique for the Temporary Control of Bleeding During Transesophageal Suture Ligation of Esophageal Varices. *R. Maurice Hood, M.D., Commander, M.C., U.S.N.*, Oakland, California 749

A Technique Employing Hypothermia for the Repair of Atrial Septal Defects. *F. John Lewis, M.D., F.A.C.S.*, Chicago, Illinois, and *Suad A. Niazi, M.B., Ch.B.*, Clarkfield, Minnesota 751

THE SURGEON'S LIBRARY

Reviews of New Books 756–760

Books Received 760

AMERICAN COLLEGE OF SURGEONS

Preliminary Plans for the 44th Clinical Congress, The Conrad Hilton Hotel, Chicago, Illinois, October 6 to 10, 1958 761

INDEX TO VOLUME 106

Contributors, Subject Matter, Book Reviews ..... i–xii

International Abstracts of Surgery

COLLECTIVE REVIEW

Benign and Malignant Adenomatous Polyps and Papillary Adenomas of the Colon and Rectum. An Analysis of 1,856 Tumors in 1,335 Patients. *Robert S. Grinnell, M.D., F.A.C.S.*, and *Nathan Lane, M.D.*, New York, New York 519–538

ABSTRACTS OF CURRENT LITERATURE

Contents [*following page 538*] ..... i–vi

Abstracts of Important Articles 539–594

Index—Abstracts, Volume 106, Subject Matter, Authors ..... i–xxxvi

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1. Bulletin of The National Research Council: Maternal Nutrition and Child Health, No. 123, (Nov.) 1950, p. 127.
2. Macy, I. G., and Hunscher, H. A.: Am. J. Obst. & Gynec. *27*:878 (June) 1934.

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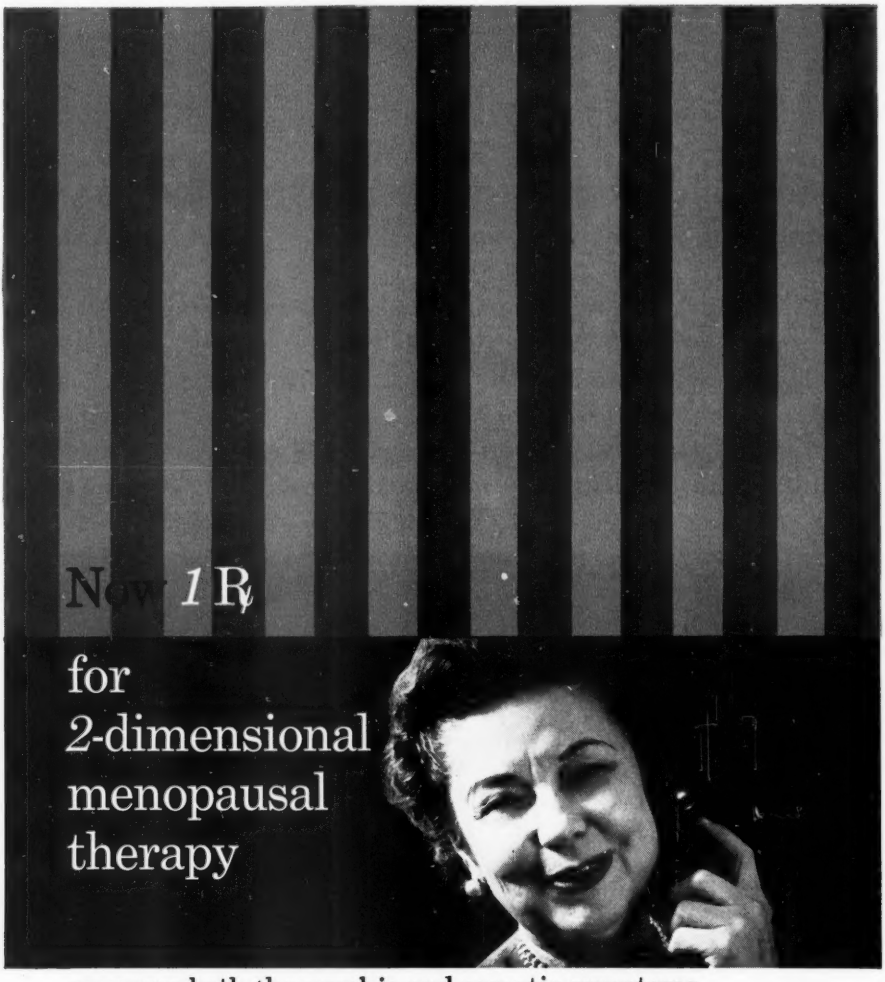

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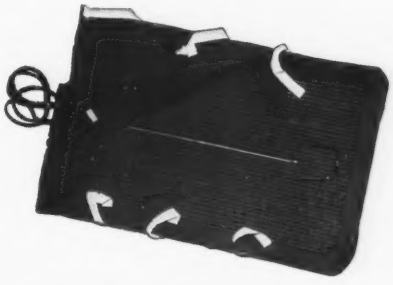

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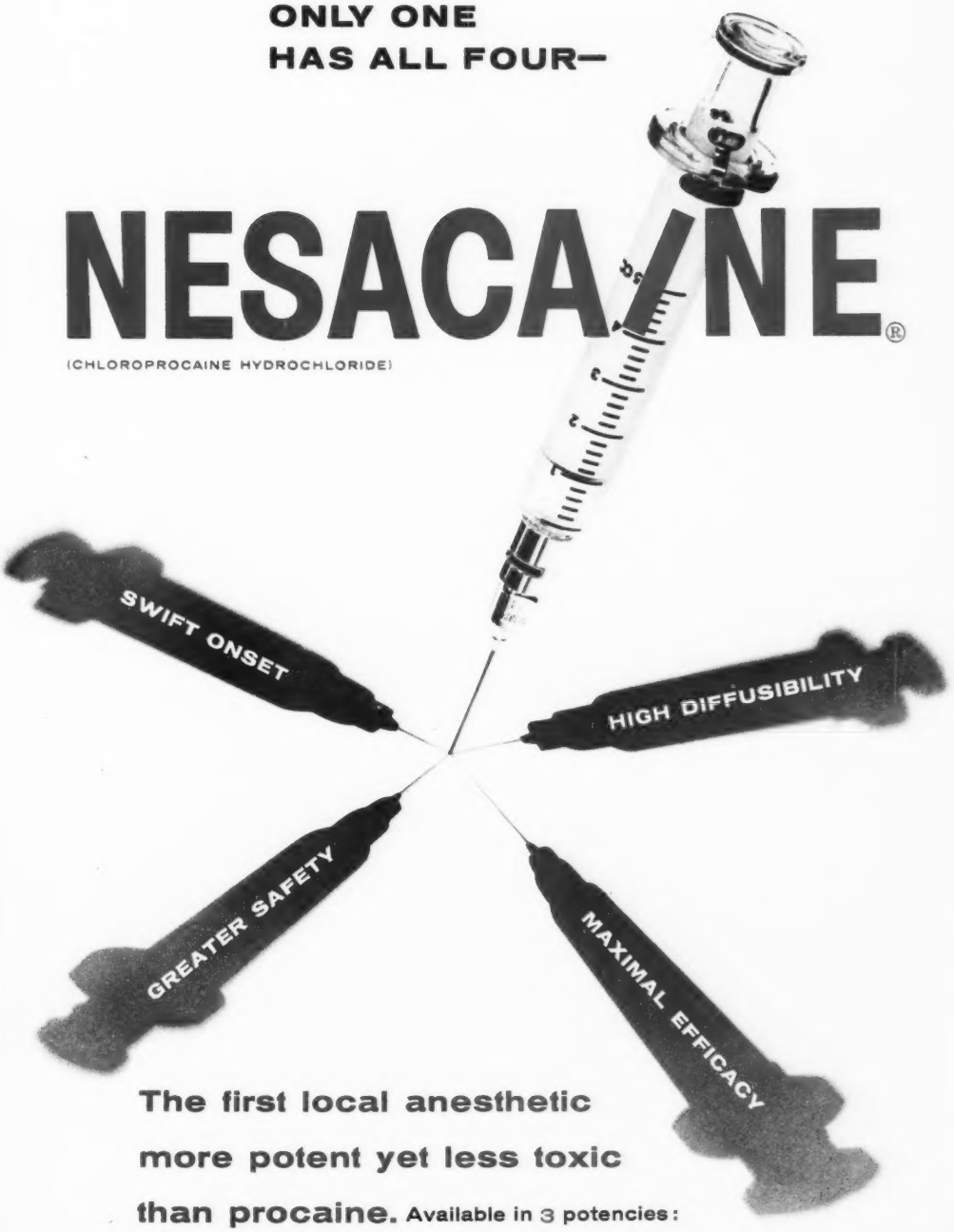

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Ansbro, F. P., and Furlong, R. E.: Adelphi Hosp. Bull. *15*:2 (May) 1957

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- **BENDING OF NEEDLES MINIMIZED OR ELIMINATED.** The point engages the tissue immediately and advancement is made with minimum effort.
- **NEEDLE HOLDER STABILITY IS MAXIMAL.** Since very little force is needed to advance the point, twisting in the holder is decreased or eliminated entirely, no matter at what angle the Deknatel 'K' Needle is held.
- **HEMOSTAT BECOMES A NEEDLE HOLDER WHEN DESIRED.** Because of the ease of passage, the excessive force of needle holder jaws is not necessary to stabilize the Deknatel 'K' Needle. Any ordinary clamping instrument will do.
- **USE OF FINER GAUGE NEEDLES THAN PREVIOUSLY POSSIBLE** because the sharpness carries the finer diameter through without bending.
- **SMALLEST DIAMETER HOLE POSSIBLE.** The Deknatel 'K' Needle point is completely within the diameter of the wire, thus making the hole of a taper point needle—the smallest one possible. There are no lateral projections of cutting sides to enlarge the hole.
- **SEMI-MALLEABILITY.** Curvature of the Deknatel 'K' Needle may be changed at will for a particular modality without increasing the danger of its breaking or bending in use.

ADDITIONAL ADVANTAGES

GENERAL SURGERY

- **FINEST APPROXIMATION OF SKIN WOUNDS.** Because of the orientation of the point, the very edges of skin are coapted with ease, producing superior cosmetic results and decreasing the scarring potential.
- **SKIN CLOSURES WITH FINER GAUGE NEEDLES THAN EVER USED BEFORE.** Closure is readily made with a 6-0 arteriovascular-type needle—a finer diameter than the equivalent ophthalmic needle. The use of finer diameters also decreases the scarring potential.
- **EXTREMELY FINE PICKUP WITHOUT TEARING OR CUTTING OUT OF TISSUE.** Subcuticular Bites: The absence of cutting sides and the orientation of the point allows the pick-up of finest sections with minimal trauma.
- **PASSING OF RETENTION SUTURES.** It is no longer necessary to 'wrestle' a needle through tissue. The extreme sharpness of the Deknatel 'K' Needle gives unusual ease of passage.
- **SAME NEEDLE FOR PERITONEUM, MUSCLE, FASCIA AND SKIN.** The absence of cutting edges on the Deknatel 'K' Needle outmodes the need for changing from taper to cutting edge needles. The Deknatel 'K' Needle is all-purpose in closure.

OB-GYN SURGERY

Mucosal layers are picked up with almost microtome thinness as in the Le Fort operation.

The needle's malleability avoids the danger of its breaking in vaginal plastic repair.

THORACIC SURGERY

- **PENETRATION OF CARTILAGE WITH SMALLEST POSSIBLE HOLE** such as costochondral junctions and trachea. A 6-0 arteriovascular needle with a Deknatel 'K' point easily penetrates the bronchus with greatly decreased probability of splitting.
- **LIGATION OF BLEEDERS ON THE SURFACE OF THE PERIOSTEUM AND TRACHEA.** Fibrous tissue will not be torn. There are no cutting sides, no cutting in or out.
- **PASSAGE THROUGH AN ARTERIOSCLEROTIC PLAQUE.** The Deknatel 'K' Needle is sharp enough and tough enough to aid greatly in the penetration of the calcification.

OPHTHALMIC SURGERY

- **IN CORNEAL AND SCLERAL WORK** the Deknatel 'K' Needle more closely approaches the ideal than any conventional cutting, reverse cutting or Grieshaber-type needles. There are no cutting sides to split fibrous tissue. There are no cutting surfaces above or below to split or cut adjacent structures. The upper flat surface picks up fibrous tissue in microtome thinness as desired.

PLASTIC SURGERY

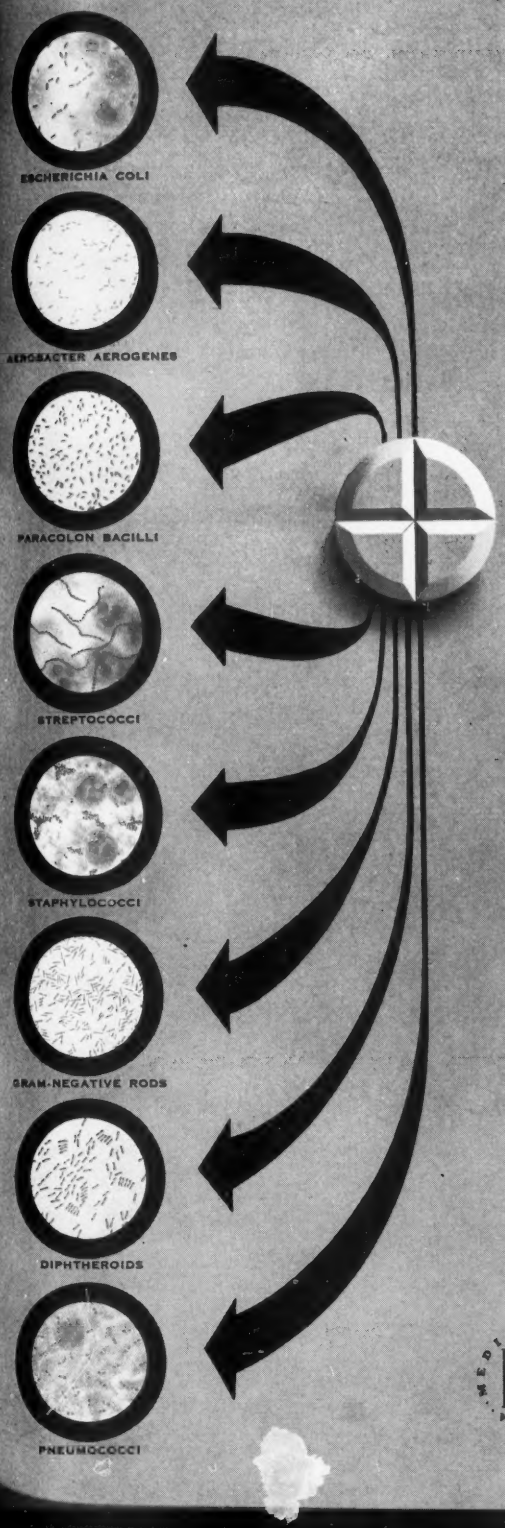
- **CLEFT PALATE.** The needle curvature may be varied into a 'V' or any other shape. The needle will not break in bending or in use.

OTOLARYNGOLOGIC SURGERY

The Deknatel 'K' Needle may be formed into a 'crochet hook' shape. There is no danger of breaking. The sharpness of the point will carry the needle through the tissue.

For samples, write –

DEKNATEL 96-32 222 STREET, QUEENS VILLAGE 29, N. Y.



new dimensions in sulfa therapy

effective sulfa levels for 24 hours with a single tablet

Midicel®

(sulfamethoxypyridazine, Parke-Davis)

wide antibacterial spectrum—effectively combats many gram-negative and gram-positive bacterial infections... valuable in genitourinary tract infections, upper respiratory infections, bacillary dysenteries, and surgical and soft tissue infections, due to sulfonamide-sensitive organisms · ***rapid effect***—therapeutic blood levels promptly attained · ***prolonged action***—effective blood and urine concentrations sustained day and night with 1 tablet daily · ***well tolerated***—high solubility and low dosage minimize possibility of crystalluria · ***1 tablet-a-day schedule***—greater convenience and economy for patients.

Adult Dosage: Initial (first day) 2 tablets (1 Gm.) for mild or moderate infections, or 4 tablets (2 Gm.) for severe infections. Maintenance—1 tablet (0.5 Gm.) daily.

Children's Dosage: According to weight. See literature for details of dosage and administration. Available: Quarter-scored tablets of 0.5 Gm., bottles of 24, 100, and 1000.

MEDICAMENTA VERA

PARKE DAVIS & COMPANY
DETROIT 32, MICHIGAN

The taste says, Yes!

BICILLIN®

ORAL SUSPENSION

STABLE!
READY TO USE!

Benzathine Penicillin G, Wyeth (Dibenzylethylenediamine Dipenicillin G)

A Superior Oral Penicillin for Children

SUPPLIED: *Cherry flavor*—300,000 units per 5-cc. tsp., bottles of 2 fl. oz.
Custard flavor—150,000 units per 5-cc. tsp., bottles of 2 fl. oz.

Wyeth®
Philadelphia 1, Pa.

PHYSICIANS' COUNCIL FOR INFORMATION ON CHILD HEALTH

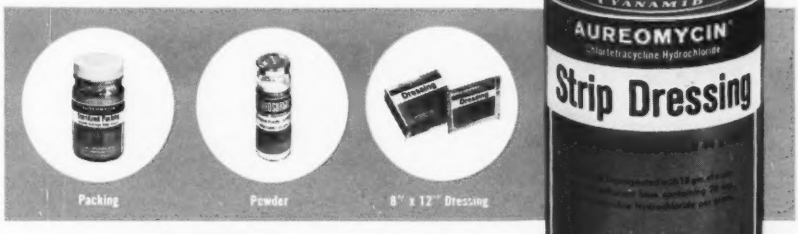
This advertisement conforms to the Code for Advertising of the Physicians' Council for Information on Child Health.

topical antibiotic therapy in its most convenient form

AUREOMYCIN®
CHLORTETRACYCLINE HYDROCHLORIDE
DRESSINGS

STERILE AUREOMYCIN DRESSINGS in 4 handy forms provide instant-ready added protection against wound infection in hospital, office or emergency use.

STERILE AUREOMYCIN DRESSINGS ensure safe, high-concentration broad-spectrum action at the site of potential or existing infection... promote faster healing and virtually eliminate odor in burns, abscesses, surgical incisions, amputations, and other wounds.



Strip Dressing

AUREOMYCIN Chlortetracycline Impregnated Gauze Products—containing 2% Chlortetracycline Hydrochloride in a special, non-adherent, water-absorbent base—are available as: Strip Dressing, ½" x 72", 2" x 108"; in glass jars. 8" x 12" Dressing, in individual aluminum foil envelopes. Packing, ½" x 24", 1" x 36", and 2" x 36"; in glass jars.

AUREOSURGIC® Surgical Powder—containing 50 mg. Chlortetracycline Hydrochloride per gram in a soluble base— is available in shaker-top bottles of 20 Gm.

CYANAMID

AMERICAN CYANAMID COMPANY
SURGICAL PRODUCTS DIVISION
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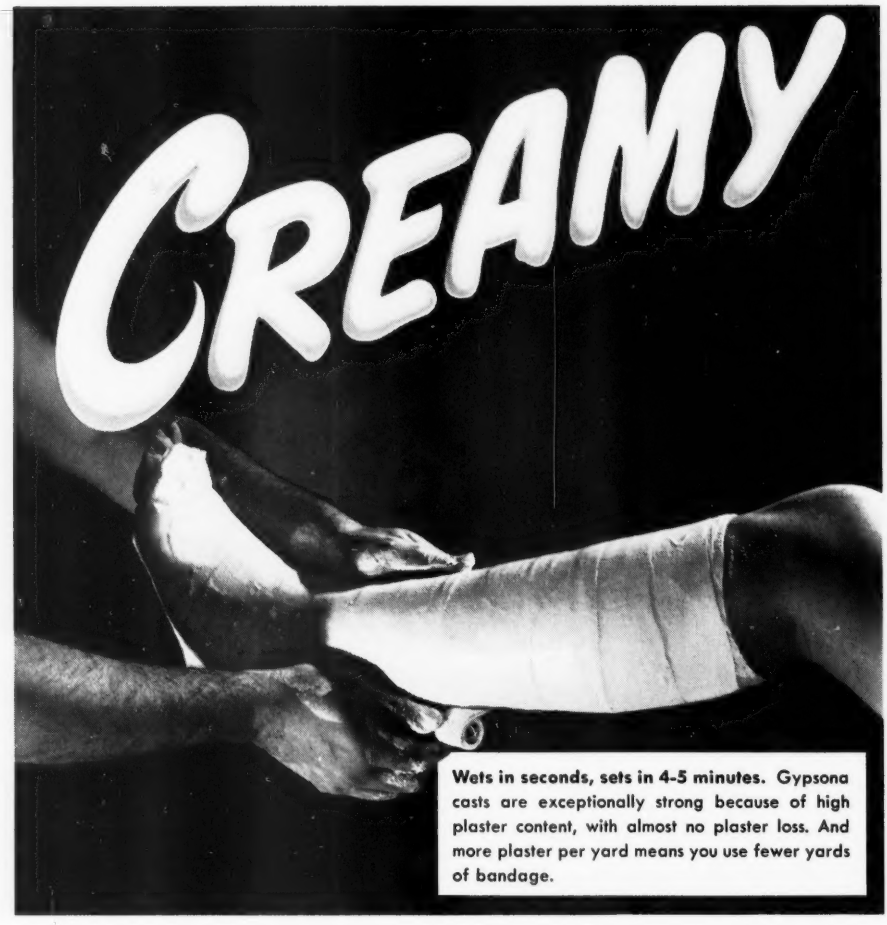
Producers of Davis & Geck Brand Sutures and
Vim Brand Hypodermic Syringes and Needles
Distributed in Canada by North American Cyanamid Ltd., Montreal 16, P.Q.


CREAMY
Wets in seconds, sets in 4-5 minutes. Gypsona casts are exceptionally strong because of high plaster content, with almost no plaster loss. And more plaster per yard means you use fewer yards of bandage.

Try Gypsona* with your own hands—here is quality you can feel

The easy workability and precise molding qualities of Gypsona have made it the most widely used plaster bandage in Europe and other parts of the world.

Now Curity makes this quality bandage conveniently available in this country.

Gypsona is made of plaster from a special quarry in England. It is purer, creamier and finer-ground than any other. Plastic core gives easy control to end of roll, will not "telescope." Waterproof package, too.

Gypsona casts are lightweight and strong, with a white, porcelain-like finish that stays neat and clean. But do see for yourself—ask your Curity representative for a demonstration.

For an appropriately fine cast padding, we direct you to WEBRIL® Bandage

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anxiety
of
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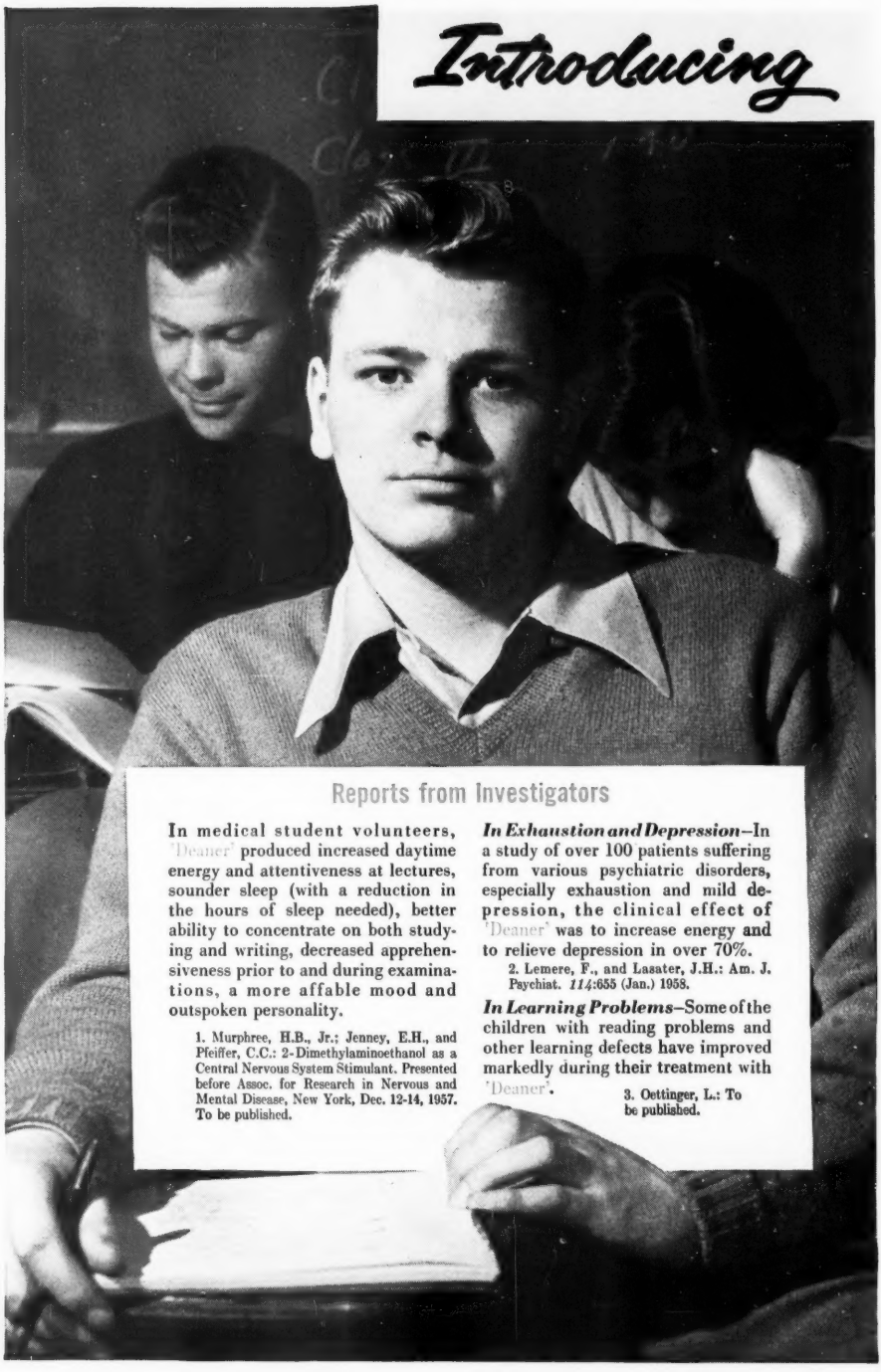
Miltown®

THE TRANQUILIZER WITH MUSCLE-RELAXANT ACTION

WALLACE LABORATORIES, *New Brunswick, N. J.*

'Miltown' relieved symptoms in 88% of pregnant women complaining of nausea, vomiting, leg cramps (refractory to calcium therapy), numbness and tingling of the extremities, headache, insomnia, anxiety, and emotional upsets.*



Reports from Investigators

In medical student volunteers, 'Deaner' produced increased daytime energy and attentiveness at lectures, sounder sleep (with a reduction in the hours of sleep needed), better ability to concentrate on both studying and writing, decreased apprehensiveness prior to and during examinations, a more affable mood and outspoken personality.

1. Murphree, H.B., Jr.; Jenney, E.H., and Pfeiffer, C.C.: 2-Dimethylaminoethanol as a Central Nervous System Stimulant. Presented before Assoc. for Research in Nervous and Mental Disease, New York, Dec. 12-14, 1957. To be published.

In Exhaustion and Depression—In a study of over 100 patients suffering from various psychiatric disorders, especially exhaustion and mild depression, the clinical effect of 'Deaner' was to increase energy and to relieve depression in over 70%.

2. Lemere, F., and Lasater, J.H.: Am. J. Psychiat. *114*:655 (Jan.) 1958.

In Learning Problems—Some of the children with reading problems and other learning defects have improved markedly during their treatment with 'Deaner'.

3. Oettinger, L.: To be published.

the Anti Depressant

Deaner™

2-dimethylaminoethanol (deanol)

A Totally New Molecule for the Treatment of

Chronic Fatigue States
Mild Depression
Chronic Headache
Migraine
Neurasthenia

In extensive clinical trials, DEANER has proved to be of value in that large contingent of patients with vague, undefined symptoms, who feel under par and lack energy or are mildly depressed.

Patients with chronic headache including migraine are benefited.

Advantages of 'Deaner'

Effects come on gradually and are prolonged . . .

Without causing hyperirritability, jitteriness or emotional tension . . .

Without causing excess motor activity . . .

Without causing loss of appetite . . .

Without elevating blood pressure or heart rate . . .

Without sudden letdown on discontinuance of therapy.

Dosage

Initially, 1 tablet (25 mg.) daily in the morning. Maintenance dose, 1 to 3 tablets (25 mg. to 75 mg.) for adults; ½ to 3 tablets for children. Full benefits may require two weeks or more of therapy.

'Deaner' is supplied in 25 mg. scored tablets in bottles of 100.

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B-P

Here it is STERILE *Rib-Back* BLADE

in the PUNCTURE PROOF Package

It's Sharp

Naturally, it can be AUTOCLAVED

Don't compromise package safety or blade quality. The B-P STERILE Rib-Back BLADE package provides both—on the outside an easily opened PUNCTURE PROOF envelope that can be autoclaved if desired . . . on the inside a STERILE Rib-Back BLADE of the same superior carbon steel you have always enjoyed.

CARBON steel—the BEST for FINE cutting edges

After all, the first consideration is cutting efficiency no matter how the blade is packaged—and cutting efficiency is exactly what you get with the 'only' B-P Rib-Back Surgical Blade, whether your preference in packaging be . . .

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BARD-PARKER RIB-BACK BLADES — ALWAYS YOUR BEST BUY IN PERFORMANCE
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Ayerst presents

NEW nonflammable, nonexplosive

"FLUOTHANE"®

(2-bromo-2-chloro-1:1:1-trifluoroethane)

A PRECISION ANESTHETIC

the most significant advance
in inhalation anesthesia
since the introduction
of ether

offered to anesthesiologists only after clinical trial in more than 20,000 cases

"Fluothane" is of outstanding significance because:

"Fluothane" provides rapid induction of anesthesia

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"Fluothane" causes minimal incidence of nausea and vomiting

"Fluothane" permits safe use of X-ray and electrocautery during anesthesia

"Fluothane" is available now to anesthesiologists. Further information on this new precision anesthetic can be obtained from the Medical Department of Ayerst Laboratories.

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"Fluothane" is supplied in the United States by arrangement with Imperial Chemical Industries, Ltd.

Metabolic demands increase when the body is subjected to surgical procedures, burns, fractures and illness. Under such circumstances, restitution of depleted vitamin reserves will accelerate body repair. STRESSCAPS provide essential water-soluble vitamins in a professionally accepted formulation.

STRESSCAPS IN STRESS

- **Infection**
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Each Capsule Contains:

Thiamine Mononitrate (B_1)	10 mg.
Riboflavin (B_2)	10 mg.
Niacinamide	100 mg.
Ascorbic Acid (C)	300 mg.
Pyridoxine HCl (B_6)	2 mg.
Vitamin B_{12}	4 mcgm.
Folic Acid	1.5 mg.
Calcium Pantothenate	20 mg.
Vitamin K (Menadione)	2 mg.

Average Dose: 1-2 capsules daily.

STRESSCAPS*

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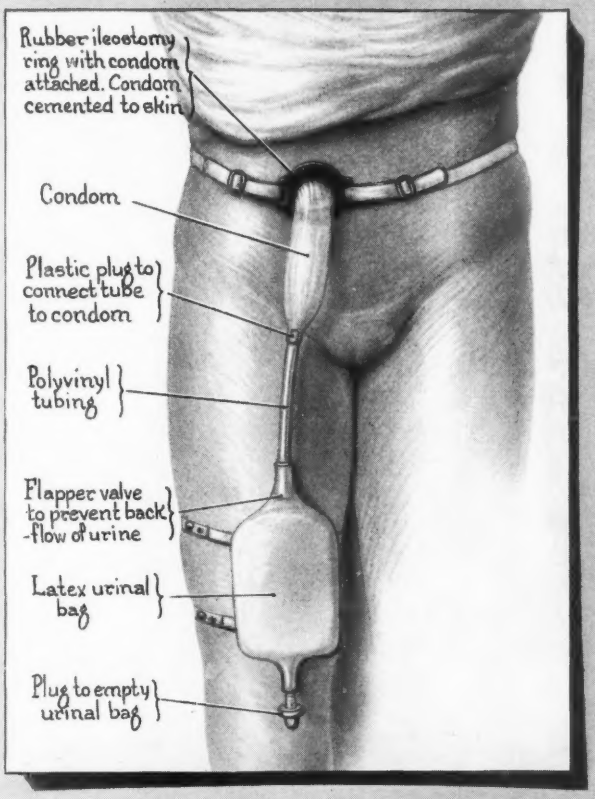
LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK

*Reg. U. S. Pat. Off.

THE LAPIDES URINARY ILEOSTOMY DEVICE* by A.C.M.I.

With the advice of patient and colleagues, this device was evolved and has proven to be efficient and reliable. It consists of a small rubber ring with belt, condom, plastic plug, polyvinyl tubing and latex urinal bag.


Rubber ileostomy ring with condom attached. Condom cemented to skin
Condom
Plastic plug to connect tube to condom
Polyvinyl tubing
Flapper valve to prevent back-flow of urine
Latex urinal bag
Plug to empty urinal bag

FEATURES

- Can be applied at operating table upon completion of ileostomy.
- Ring-condom-skin arrangement allows easy removal and replacement.
- Condom is only replacement necessary in device.
- Condom stretches and acts as a safety valve. If tubing or urinal bag becomes occluded, urine can still be pumped by ileum into condom without appreciably increasing intra-ileal or intra-ureteral pressures and without forcing the device from the skin.
- The large diameter of the hole in the ileostomy ring provides a wide margin of skin between the inner edge of the ring and the ileostomy. This prevents pressure necrosis of the ileum and also permits easier application of the ring to the skin.
- It is neat and streamlined permitting the patient to wear form-fitting clothes.

Consult Your Dealer
or
Write For Informative Reprint

Cat. No. 2769

**A Urinary Ileostomy Device by Jack Lapides, Robert Boyd and Sheldon L. Fellman from the Department of Surgery, University of Michigan Medical Center, Veteran's Administration Hospital, Ann Arbor, Michigan and Wayne County General Hospital, Eloise, Michigan.*

ESTABLISHED IN 1900 BY REINHOLD WAPPLER
FREDERICK J. WALLACE, President
American Cystoscope Makers, Inc.
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high blood levels, reliable blood level

CYCLA

Triacetyloleandomycin, Wyeth

Effective against many organisms resistant to other agents

Effective against many common infections of everyday practice

Acid-resistant, readily absorbed, effectively utilized

Reliable blood levels—rapid, high, sustained

Low incidence and minimal severity of sensitivity and toxic reactions

Wyeth

YCLAMYCIN is a new, orally effective antibiotic derivative. Clinical trials monstrate extensive applications in treatment and specific usefulness problems of antibiotic resistance and reactions.

CYCLAMYCIN antimicrobial spectrum encompasses most gram-sitive and some gram-negative bacteria. It is effective in many infec-ons caused by organisms resistant to erythromycin, the tetracyclines, enicillin, and streptomycin. It is particularly useful against many re-stant strains of staphylococci in hospital populations.

MYCIN*

CAPSULES • ORAL SUSPENSION

CYCLAMYCIN is notably well-tolerated. Clinical experience shows a low ncidence and minimal severity of sensitivity or untoward reactions. This s an advantage of pronounced importance for patients with a history f toxicity or hypersensitivity to other agents.

Favorable response to CYCLAMYCIN has followed its use in a wide variety f both minor and serious infections. These conditions include:

Staphylococcal infections: Abscesses, infected cysts, impetigo, fected ulcers and wounds, furuncles, carbuncles, cellulitis, urinary-ract infections.

Streptococcal infections: Streptococcal pneumonia, cellulitis, tonsil-s, pharyngitis, infections of traumatic and surgical wounds, urinary-ract infections.

Pneumococcal infections: Lobar pneumonia, bronchial pneumonia.

Haemophilus influenzae infections: Pneumonia.

Supplied: Capsules, 125 mg. (gray and yellow) and 250 mg. (black and yellow), vials of 36. Suspension (cherry-raspberry flavored), 125 mg. per 5-cc. teaspoonful, bottles of 2 oz. Also available: Oleandomycin Phosphate, Wyeth, for intravenous administration—as dry powder for reconstitution; each vial contains 500 mg. of oleandomycin base as the phosphate salt.

*Trademark

in these conditions *peritonitis, mixed infections of the urinary tract, as a supportive measure in surgery, and in selected cases of bacterial endocarditis*

the combination *of penicillin and dihydrostreptomycin is*

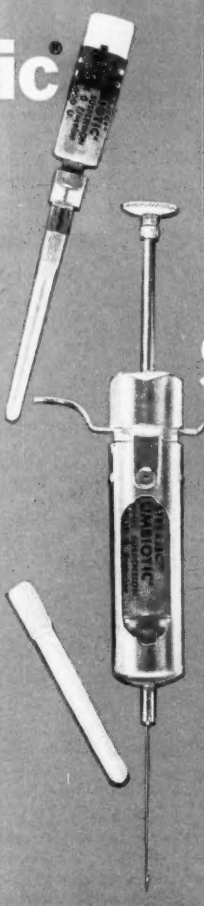
therapy of choice *One injection from one vial*

Combiotic®

COMBIOTIC P-S (DRY POWDER) 1.0 Gm. Formula: 300,000 units penicillin G procaine crystalline, 100,000 units penicillin G potassium crystalline, 1.0 Gm. dihydrostreptomycin sulfate, per dose.

COMBIOTIC P-S (DRY POWDER) 0.5 Gm. Formula: same penicillin content as above, but with 0.5 Gm. dihydrostreptomycin sulfate per dose.

COMBIOTIC AQUEOUS SUSPENSION (ready to inject) in five-dose "drain-clear" (10 cc.) vials, 400,000 units penicillin G procaine crystalline and 0.5 Gm. dihydrostreptomycin sulfate, in each 2 cc. dose.



Combiotic Aqueous Suspension also available in one injection from one cartridge

Steraject®

single-dose disposable cartridge with sterile needle attached — use and dispose — eliminates sterilization, measuring, assembly, breakage.

Pfizer injectables available in single-dose disposable cartridges:

PENICILLIN G PROCAINE CRYSTALLINE IN AQUEOUS SUSPENSION, 300,000; 600,000 and 1,000,000 units.

COMBIOTIC AQUEOUS SUSPENSION, 400,000 units penicillin G procaine crystalline plus 0.5 Gm. dihydrostreptomycin.

STREPTOMYCIN SULFATE SOLUTION, 1 Gm.

DIHYDROSTREPTOMYCIN SULFATE SOLUTION, 1 Gm.

(smaller, 22-gauge needle for most dosage forms minimizes injection pain)

Pfizer PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y.

The most effective treatment known for dandruff

ABBOTT LABORATORIES

SELSUN®

(Selenium Sulfide, Abbott)

2 IBEROL Filmtabs a day supply:

THE RIGHT AMOUNT OF IRON

Ferrous Sulfate, U.S.P. ..... 1.05 Gm.
(Elemental Iron—210 mg.)

PLUS THE COMPLETE B COMPLEX

BEVIDORAL® .....1 U.S.P. Unit (Oral)
(Vitamin B_{12} with Intrinsic Factor Concentrate, Abbott)
Folic Acid ..... 2 mg.
Liver Fraction 2, N.F. ..... 200 mg.
Thiamine Mononitrate ..... 6 mg.
Riboflavin ..... 6 mg.
Nicotinamide ..... 30 mg.
Pyridoxine Hydrochloride ..... 3 mg.
Calcium Pantothenate ..... 6 mg.

PLUS VITAMIN C

Ascorbic Acid ..... 150 mg.

anemia in convalescence

another indication for filmtab® Iberol®

potent antianemia therapy
plus the complete B-complex

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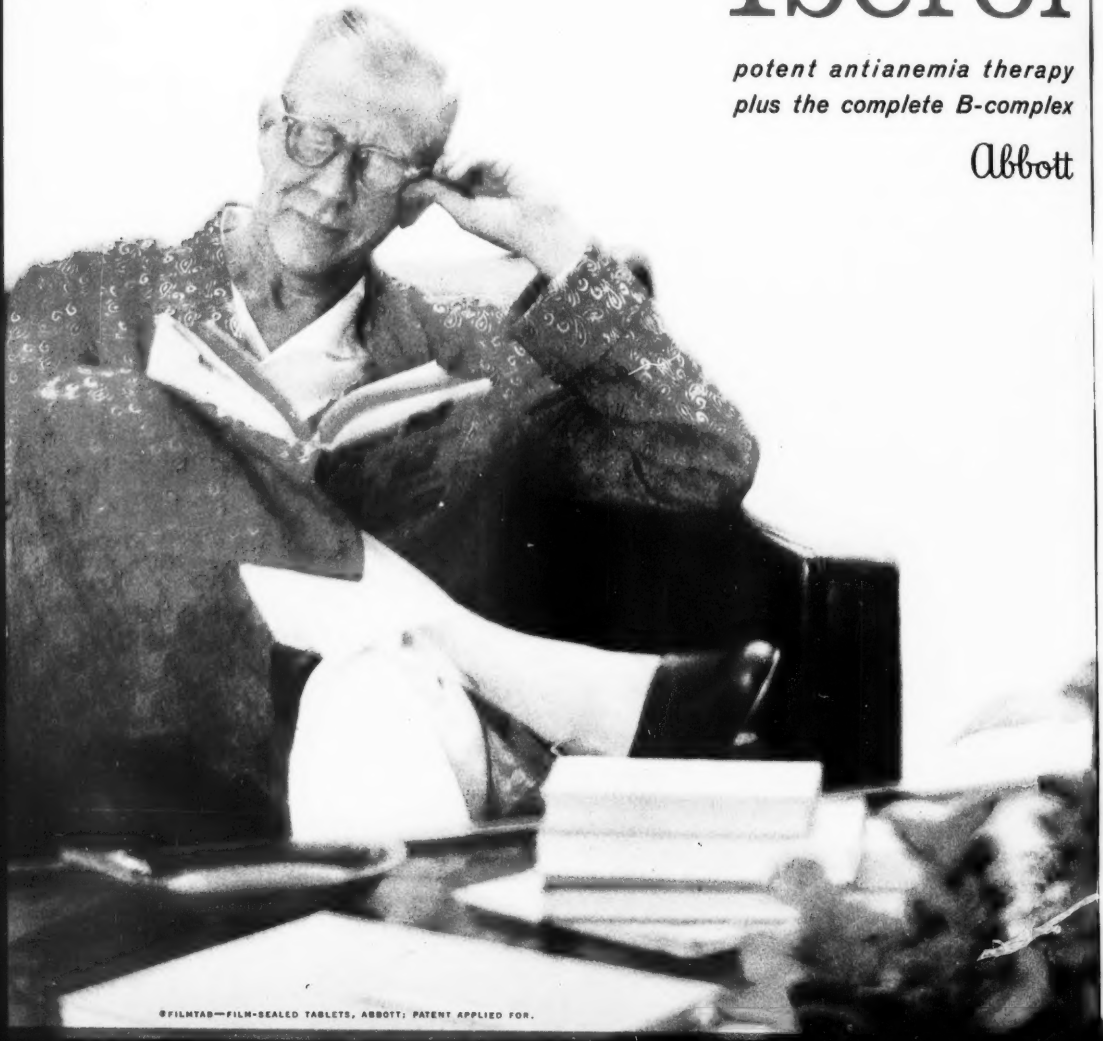
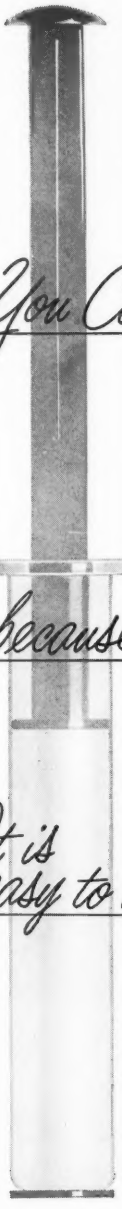


®FILMTAB—FILM-SEALED TABLETS, ABBOTT; PATENT APPLIED FOR.

increasing monilial vaginitis
demands faster,
more specific therapy



You Can

STOP vulvar itching and burning faster

GET quicker cures . . .

with

gentia·jel®

the true specific for monilial vaginitis

because

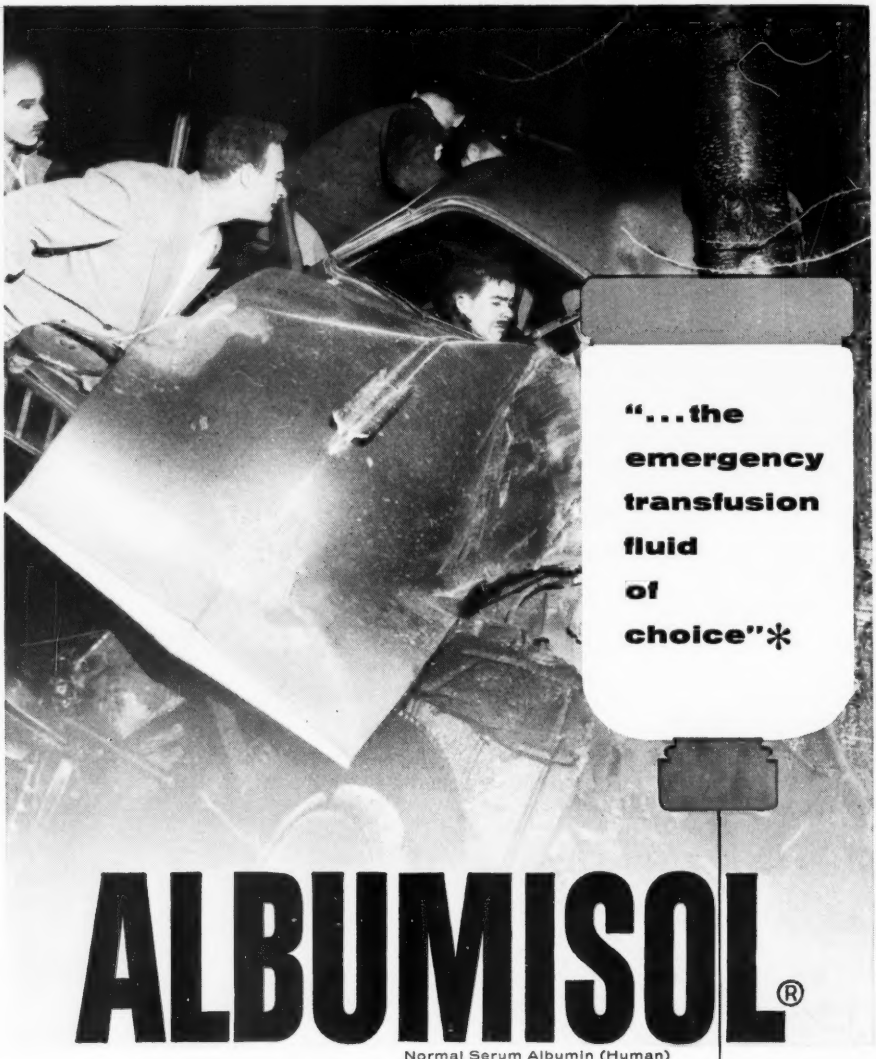
Gentia-jel provides an unsurpassed monilial killing gel which disperses completely over the vaginal and cervical mucosa . . . penetrates into all folds . . . and bathes the vulvar labia. This soothing fungus and bacteria destroying gel provides fast gratifying relief of vulvar itching and burning, and results in quicker cures.

It is easy to use

Have the patient follow these simple steps: (1) Insert applicator and instill Gentia-jel on retiring. (2) Remove and discard applicator, place a pledget of cotton in the introitus and wear a perineal pad.

Supplied
In packages of 12 single-dose disposable applicators.

Westwood Pharmaceuticals
Division of Foster-Milburn Co. · Buffalo 13, New York



ALBUMISOL®

Normal Serum Albumin (Human)

No risk of serum hepatitis
Ready for administration; no storage problems
Human protein; readily metabolized
Contains no blood-clotting components
No grouping, typing, cross-matching required

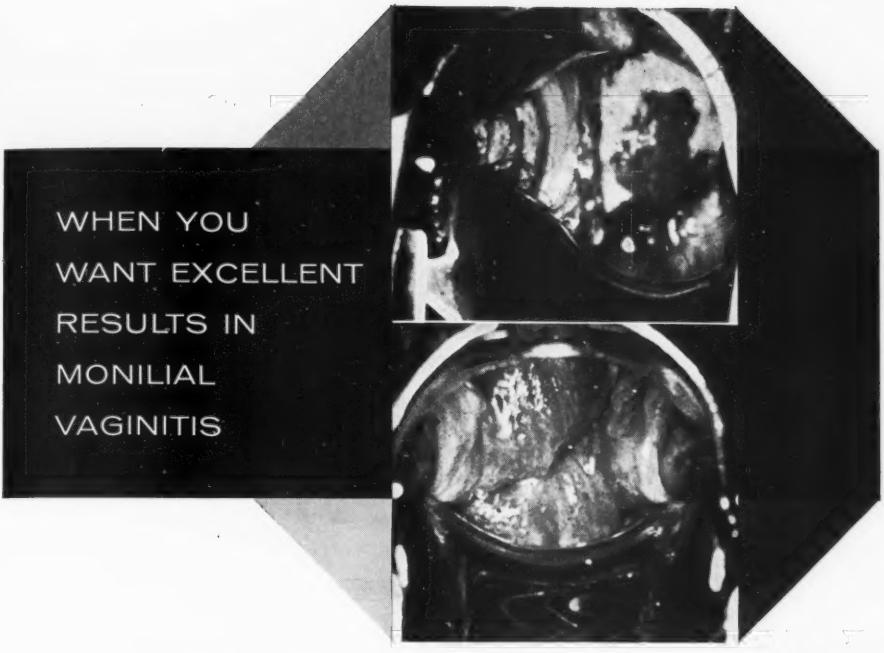
Supplied: 'ALBUMISOL' 5%—in 250 and 500 cc. bottles in packages with a set of disposable intravenous equipment.

Also supplied: 'ALBUMISOL' 25% (Salt-Poor)—in 20 cc. bottles; in 50 cc. bottles in packages with a set of disposable intravenous equipment.

*Janeway, C.A.: Quart. Rev. Med. **9**:153 (Aug.) 1952.

MSD

MERCK SHARP & DOHME
Division of MERCK & CO., INC.
Philadelphia 1, Pa.



MYCOSTATIN

VAGINAL TABLETS

Squibb Nystatin

RESULTS:
"Of 96 patients with records suitable for tabulation, 85 had from good to excellent results."[1] In a group of 13 pregnant and 12 nonpregnant clinic patients "all patients were rapidly relieved of their symptoms, within 24 hours in most cases. . . . The writer has seldom been so rapidly convinced of the value of a new therapeutic agent."[2]

Mycostatin is the safe, highly effective antifungal antibiotic . . . with direct, specific action against monilia. When you use Mycostatin Vaginal Tablets for your patients with monilial vaginitis, your therapy can be 98.3% successful.[3] And your treatment will be clean—*without messiness or staining*—a point your patients will appreciate.

Each tablet contains 100,000 units of Mycostatin and 0.95 Gm. lactose. Packages of 15 with applicator; packages of 100 without applicator. Each tablet individually foil wrapped.

Therapy: 1 tablet intravaginally once to twice daily for 2 weeks, or as required.

You can also use Mycostatin Oral Tablets; Mycostatin Ointment; Mycostatin Dusting Powder; Mycostatin for Suspension.

1. Thomas, H. H.: Obstet. & Gynec. 9:163, 1957. 2. Browne, A. D. H.: J. Irish M.A. 40:86, 1957. 3. Pace, H. R., and Schantz, S. I.: J.A.M.A. 162:268, 1956.

"MYCOSTATIN"® IS A SQUIBB TRADEMARK

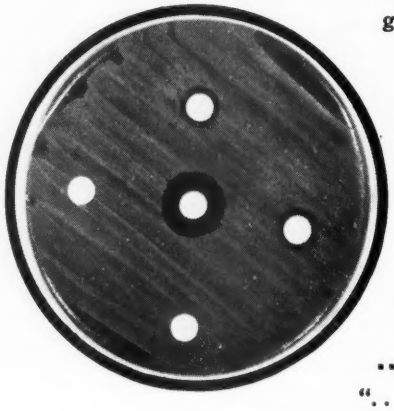
SQUIBB

SQUIBB QUALITY—
THE PRICELESS
INGREDIENT

on the problem of ai

A POINT OF VIEW IN '55

"At this time, it appears that the problem of antibiotic-resistant bacteria is the greatest fear in the future with chronic infections of the . . . urinary tract . . ."[1]



A POINT OF FACT IN '58

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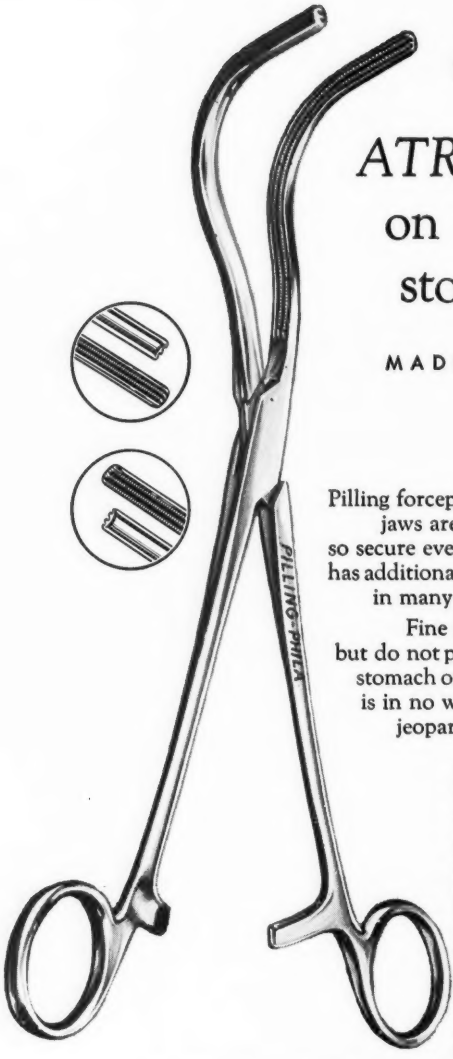

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Wilkins, R. W.: New England J. Med. **257**:1026, Nov. 21, 1957.

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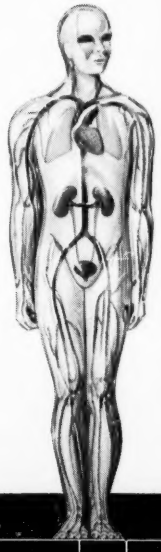

Freis, E. D., Wanko, A., Wilson, I. H. and Parrish, A. E.: J.A.M.A. **166**:137, Jan. 11, 1958.

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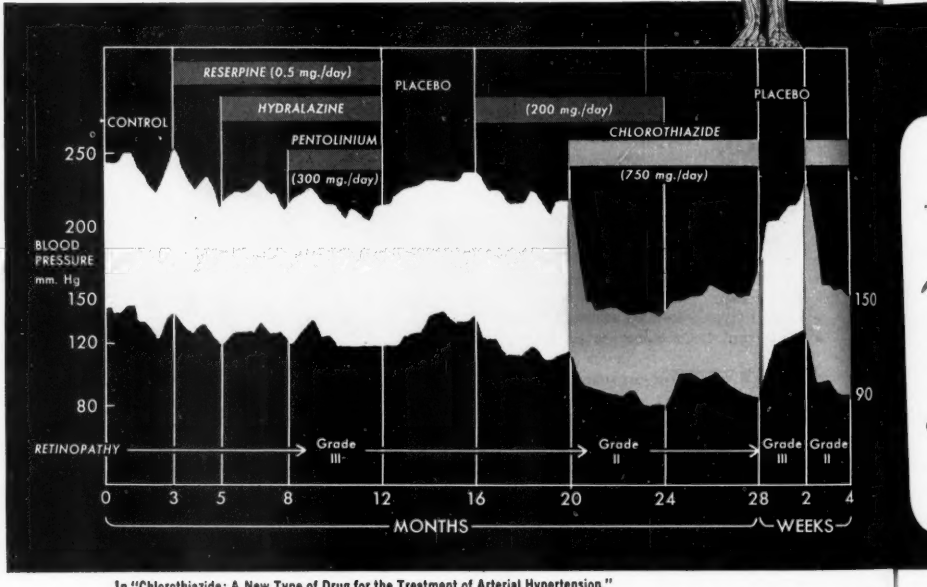

In "Chlorothiazide: A New Type of Drug for the Treatment of Arterial Hypertension," Hollander, W. and Wilkins, R. W.: Boston Med. Quart. **8**: 1, September, 1957.

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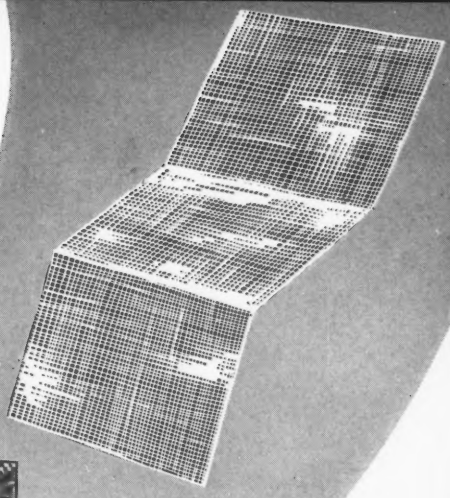

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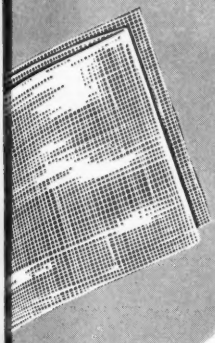

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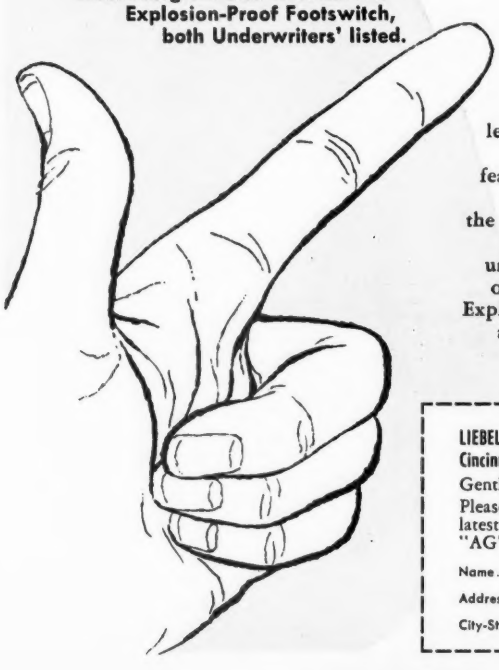

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sources: (1) Steinberg, W.: Am. J. Obst. & Gynec. 75:144, 1958.
(2) Becker, S.: J. Am. M. Women's A. 12:332, 1957

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(1) Hagedorn, A. B.: Proc. Staff Meet. Mayo Clin. 32:705 (Dec. 11) 1957.
(2) Best, W. R.; Louis, J., and Limarzi, L. R.: M. Clin. North America (Jan.) 1958, p. 3.

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Figure 1 *(above)*—Lateral radiograph of knee area in a case of pigmented villonodular synovitis in a man of 53 years. Note the lobulated soft-tissue masses posteriorly and the effects of invasion of the patella and the femoral condyles by lesional tissue.

PIGMENTED VILLONODULAR SYNOVITIS
. . . 3 aspects

Figure 2 *(above)*—Photograph of a portion of the resected synovium with attached menisci from the case shown in Figure 1. Note the deep brownish color of parts of the villously hypertrophied synovium.

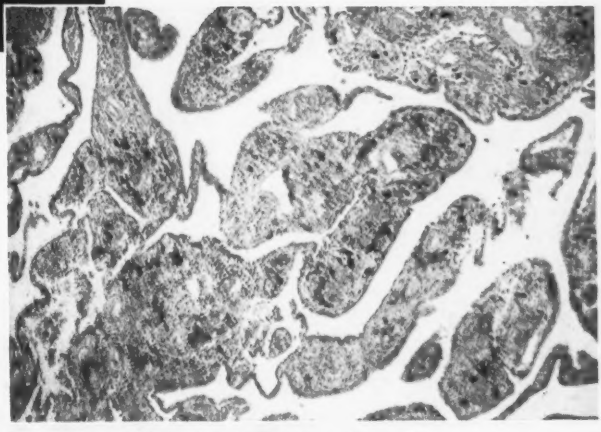

Figure 3 *(right)*—Photomicrograph (x 25) showing a tissue area in a villonodular synovitis in which the proliferated villi are matted together. The brownish discoloration of the tissue is due to hemosiderin pigment.

Turn page for data on Synovial Osteochondromatosis . . . 3 aspects

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SYNOVIAL OSTEOCHONDROMATOSIS . . .
3 aspects

Figure 1 *(above)*—A lateral radiograph from a case of synovial osteochondromatosis of the knee. Note the faint opacities in the suprapatellar pouch area and in the posterior compartment.

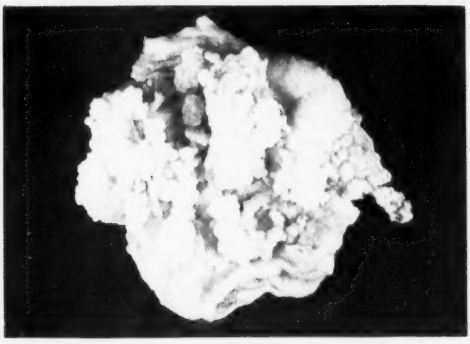

Figure 2 *(above)*—Photograph showing the synovial surface of the suprapatellar pouch. Note the cartilaginous excrescences, many of which are protruding from the surface.

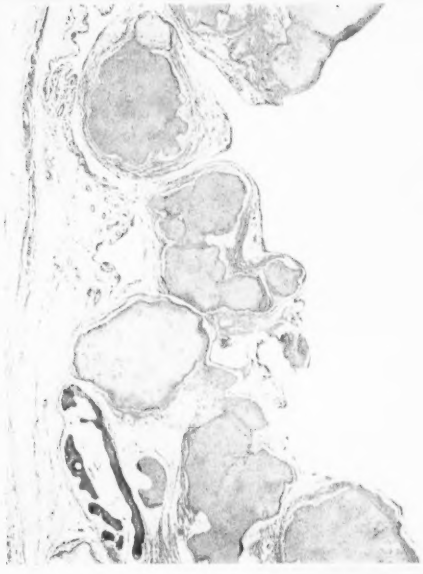

Figure 3 *(right)*—Photomicrograph (x 3) of representative section prepared from lesional tissue shown in Figure 2. Note the numerous islands of cartilage within the synovial membrane. Some are agglomerated and are protruding into the pouch.

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1. Kinney, J. J.: J. M. Soc. New Jersey 53:128, 1956.

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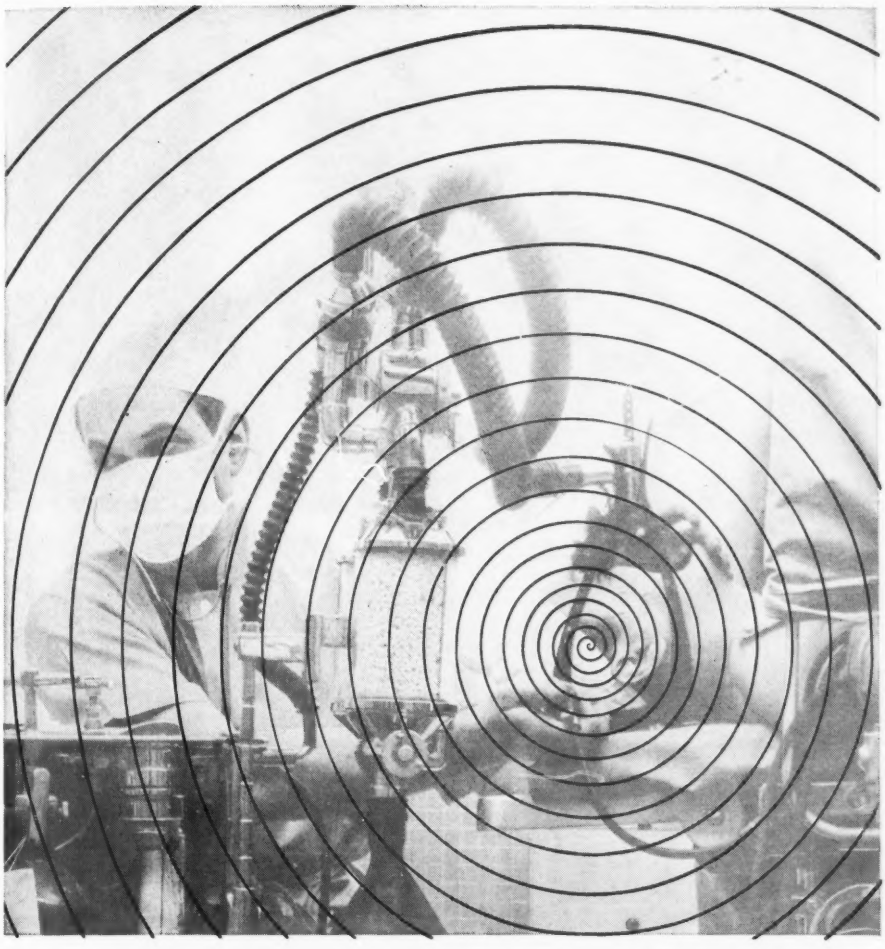

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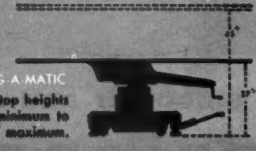

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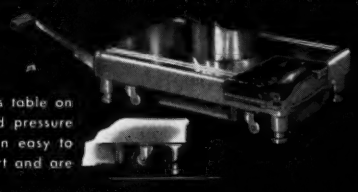

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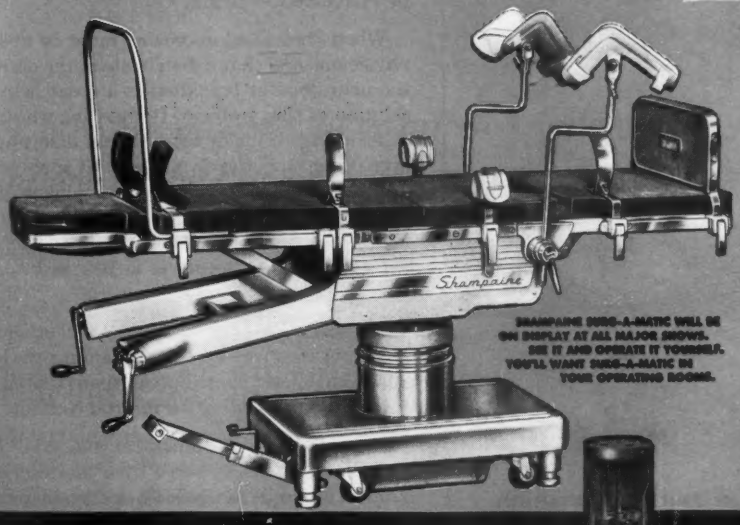

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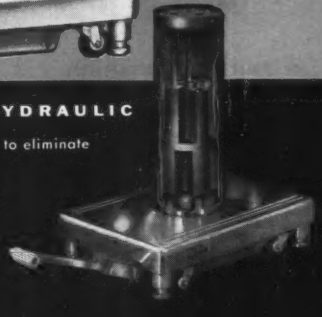

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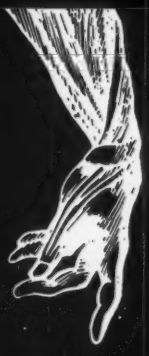

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		"marked"	moderate	slight	none
STUDY 1[1]					
Skeletal muscle spasm secondary to acute trauma	33	26	6	1	—
		"pronounced"			
STUDY 2[2]					
Herniated disc	39	25	13	—	1
Ligamentous strains	8	4	4	—	—
Torticollis	3	3	—	—	—
Whiplash injury	3	2	1	—	—
Contusions, fractures, and muscle soreness due to accidents	5	3	2	—	—
		"excellent"			
STUDY 3[5]					
Herniated disc	8	6	2	—	—
Acute fibromyositis	8	8	—	—	—
Torticollis	1	—	—	1	—
		"significant"			
STUDY 4[6]					
Pyramidal tract and acute myalgic disorders	30	27	—	2	1
TOTALS	138	104 (75.3%)	28 (20.3%)	4	2

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SURGERY
Gynecology & Obstetrics

JUNE 1958
VOLUME 106
NUMBER 6

LYMPHOID POLYPS (BENIGN LYMPHOMA) OF THE RECTUM AND ANUS

FRED HOLTZ, M.D., and LEWIS A. SCHMIDT, III, M.D., Ann Arbor, Michigan

SO-CALLED BENIGN LYMPHOMA of the rectum is an uncommon, usually solitary, polypoid lesion of the lower rectum or anus, composed of lymphoid follicles which are limited to the mucosa and submucosa. The pathogenesis has not been determined and the chief importance of the condition is that it may be diagnosed erroneously as malignant lymphoma. In the literature some cures of malignant lymphoma primary in the rectum are reported.

Synonyms for this rectal lesion are lymphoid polyp, polyp of lymphatic tissue, lymphoma, simple lymphoma, abnormal accumulation of lymphoid follicles, primary lymphoid tumors of the rectum resembling internal hemorrhoids, and benign lymphoid hyperplasia of the rectum.

MATERIALS AND METHODS

All of the noncarcinomatous or nonadenomatous polyps of the rectum and anus seen in the Department of Pathology of the University of Michigan Medical Center, from July 1, 1935 to June 30, 1955 were reviewed. All lesions not associated with ulcerative colitis were examined histologically and 24 cases met the criteria of "benign lymphoma" or lymphoid polyp.

From the Department of Pathology and the Department of Surgery, University of Michigan Medical School and Hospital, Ann Arbor, Michigan.

During this same period, 7 examples were diagnosed as malignant lymphoblastoma primary in the rectum. None of the cases now designated benign lymphoma or lymphoid polyp had been considered malignant at the time of initial diagnosis in contrast to 50 per cent of those in the series of Helwig and Hansen.

The earliest cases in the English medical literature were reported in 1890 by Shattock and Ball, and except for reports by Greig in 1908, Dukes in 1933, and Hayes, Burr, and Pruit in 1940, the condition generally was ignored. Since 1945, numerous reports have appeared so that Hayes and Burr were able to collect 206 cases from the literature in 1952.

One feature which has delayed establishing the exact nature of the process is a lack of sufficient long term follow-ups in reported cases. In 1948, Li found that only 5 of 49 cases previously reported had been followed up 5 or more years, and only 12 of 70 cases reported by Helwig and Hansen had been followed up 5 or more years. Hayes and

FIG. 1. Benign lymphoma illustrating the atrophy of the overlying mucosa in Case 3. ×107.

Burr reported 13 of 22 cases followed up 5 or more years.

The reported incidences of these polyps varies from 3 per cent of 259 anorectal tumors reviewed by Heller and Lewis to 14.6 per cent of 363 cases of anal and rectal tumors reviewed by Ehrlich and Hunter.

While most reported cases have occurred in adults from 20 to 50 years of age, they have appeared in all age groups including children. There is no apparent predisposition for sex.

AGE AND SEX

Of the 24 patients with "benign lymphomas" in our material, 16 were females and 8 were males. They ranged in age from 21 to 64 years with the greatest concentration in the fourth decade (Table I). The mean age was 42.1 years.

TABLE I.—AGE AND SEX

Age, years	*Males*	*Females*	*Total*
20–29	2	1	3
30–39	4	6	10
40–49		4	4
50–59	1	3	4
60–69	1	2	3

SYMPTOMS

In this series of 24 patients, the analysis of the symptoms is of interest. Sixteen patients complained of rectal bleeding, which varied in frequency from an occasional streaking of the stool to a loss of one-half cupful of blood with each stool. Constipation was the next most frequent complaint reported by 9 patients; and only 1 patient complained of diarrhea. A mass was detected on routine physical examination in 8 patients, while in 3 others a mass protruded at defecation. Seven patients complained of vague rectal pain. In 8 patients there were concomitant hemorrhoids and 1 patient had colonic diverticulosis. No abnormal hematologic findings suggesting a malignant lymphoma or leukemia were recorded.

The polyps varied from 5 millimeters to 3 centimeters in diameter and occurred from the level of the anal sphincter to 14 centimeters above this area. In 6 cases polyps were observed; however, in no case were more than 3 reported.

The microscopic features included hyperplastic lymphoid follicles with prominent germinal centers in the mucosa and submucosa of the anus or rectum. There was no encapsulation of the lymphoid foci, and the follicles were separated by strands of reticulin. Frequently, the follicles encroached upon the muscularis mucosae and atrophy of the overlying mucosa was common; however, invasion of the muscularis propria did not occur. Mitotic figures were frequent in the germinal centers but were not seen elsewhere. Phagocytosis by cells of the germinal centers frequently was noted and resembled that seen in tonsils. In 2 instances, the polyps were covered in part by squamous epithelium.

In contrast, the malignant lymphoblastoma primary in the rectum showed a complete loss of follicular architecture except for a few persistent follicles in 2 cases designated giant follicular lymphoma. In the

TABLE II.—FOLLOW-UP STUDIES

Case No.	Date of treatment	Age, years	Sex	Follow-up	Years
1	12-11-35	43	F	Died 9-24-46, rheumatic fever	10-9/12
2	8-28-36	58	F	Living and well 4-14-57	20-8/12
3	11-20-36	44	F	Living but like symptoms, 8-5-57	20-8/12
4	3- 8-38	34	M	Lost	
5	4-21-38	37	M	Lost	
6	12-20-38	58	F	Died 8-10-53, carcinoma of larynx	14-8/12
7	2-28-40	39	F	Well 1-24-57	17
8	10-10-40	46	F	Well May, 1957	16-7/12
9	1-22-43	35	F	Well May, 1957	14-4/12
10	2-16-45	34	F	Well May, 1957	12-3/12
11	3-16-45	55	F	Well May, 1957	12-2/12
12	1-20-47	25	M	Well January, 1957	10
13	7-18-47	57	M	Well May, 1957	9-10/12
14	2-12-48	35	M	(Biopsy only.) Well March, 1957	9-1/12
15	4-30-48	21	M	Well May, 1957	9
16	5-18-48	31	F	Well May, 1957	9
17	5-24-49	33	F	Well May, 1957	8
18	11-29-49	60	F	Died 11-19-51, dissecting aneurysm	2
19	8-25-50	61	F	Well March, 1957	6-7/12
20	1-23-51	64	M	Well March, 1957	6-2/12
21	2-14-52	29	F	Well March, 1957	5-3/12
22	1- 7-53	42	F	Well March, 1957	4-4/12
23	11-20-53	38	F	Lost	
24	12-10-54	33	M	Well November, 1957	3

malignant lymphoblastomas, invasion of the underlying muscularis propria was common and involvement of regional lymph nodes frequent. Mitotic figures were scattered throughout the areas of lymphoid infiltration and phagocytes were not noted in any of the 7 malignant lymphoblastomas primary in the rectum.

The pathogenesis of so-called benign lymphomas is not precisely known and three theories have been proposed: (1) they are a manifestation of the thymicolymphatic constitution; (2) they are true neoplasms but benign; (3) they are inflammatory.

If they were a manifestation of the thymicolymphatic constitution it would seem reasonable to expect a greater incidence in children than in adults. In adults lymphoid tissue is normally involuting with the exception of struma lymphomatosa which occurs in adult females of this age group. In addition, if it were a constitutional liability one would anticipate multiple lesions as described by Goldman.

Evidence in favor of a neoplastic nature is that they are usually solitary polyps and,

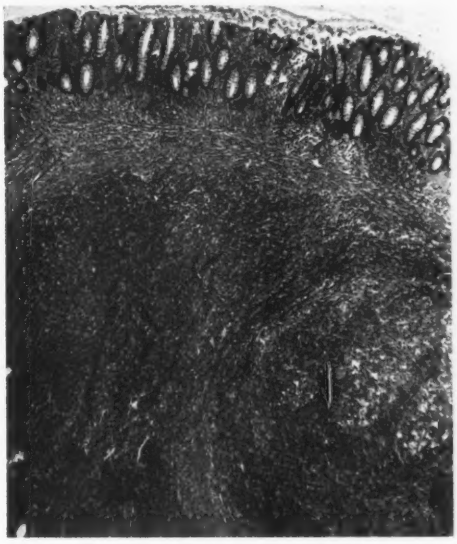

FIG. 2. Benign lymphoma showing follicles with germinal centers in submucosa in Case 9. ×14.

according to Heller and Lewis, without evidences of inflammation in adjacent tissues, a generally intact mucosa, and no significant fibrosis. Against a neoplastic nature is the fact that no well documented example has become malignant. Also lesions have been reported to regress with incomplete removal of the lesion, and no lesions have re-

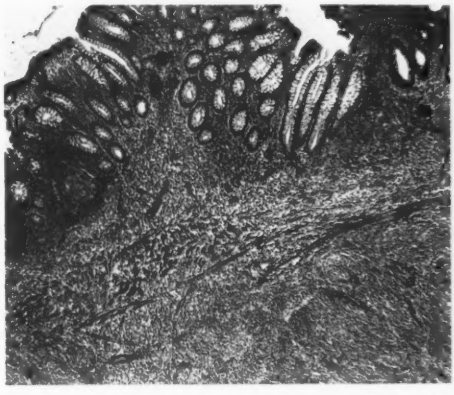

FIG. 3. Benign lymphoma illustrating infiltration of muscularis mucosae, submucosa, and mucosa by lymphocytes. Also follicle formation in Case 8. ×18.

curred after removal. The frequent association of rectal bleeding, protrusion of the lesion, and constipation as reported by Heller and Lewis suggest that mild physical and chemical trauma may be causative. In addition Helwig and Hansen noted fibrosis and eosinophiles in a few of their examples, while Smith reported an ulcer associated with the lymphoid tissue. Except for struma lymphomatosa, other benign diseases characterized by lymphoid hyperplasia with discrete follicle formation commonly are regarded as inflammatory.

After examining many rectal biopsies, a mode of pathogenesis was suggested. This is that there was a pre-existing mucosal fold in the rectum or anus, perhaps a hypertrophic anal papilla, which was subjected to repeated minor physical and chemical trauma during defecation. Initially there were small infiltrations of lymphocytes in the mucosa and submucosa, and perhaps follicles were normally present. With continued irritation more follicles were formed and a so-called benign lymphoma resulted. Thus, on a morphologic basis, this lesion may be essentially an inflammatory response in a pre-existing rectal or anal fold or papilla, but the possibility of constitution determining the type of inflammatory response cannot be excluded. The suggestion of Helwig and Hansen, Granet, Kagan, and Solomon, Sniderman, and Gruenwald as to the essential nature of the process is acceptable but the sharp localization may be due to pre-existing rectal or anal folds or other minor anatomic abnormalities.

FOLLOW-UP

Of the 24 cases studied, 21 patients were contacted for follow-up studies (87.5 per cent) (Table II). Seventeen patients are alive and asymptomatic 20.7, 17, 16.5, 14.3, 12, 12, 10, 10, 9, 9, 9, 8, 6.5, 6, 5, 4.5, and 2.5 years after therapy. Three patients died 10.7, 14.7, and 2 years after removal of their lesions, but there was no clinical evidence of recurrence in these patients. One died of rheumatic heart disease and 1 of carcinoma of the larynx; the last died of dissecting aneurysm. One patient is alive 20.7 years later but has complained of a recurrence of symptoms for several years. Three were lost to follow-up.

SUMMARY

A histologic study of 24 cases of lymphoid polyps resulted in the conclusion that these lesions are the result of chronic inflammation, possibly at the sites of minor anatomic abnormalities. The benign nature was confirmed by follow-up studies in 21 of the 24 cases.

The term lymphoid polyp may be preferable to the term benign lymphoma.

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FAILURE OF MIGRATION OF THE RECTAL OPENING AS THE CAUSE FOR MOST CASES OF IMPERFORATE ANUS

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IN REVIEWING a series of 70 cases of anorectal anomalies which we have been privileged to see during the course of the past 9 years, we have found that in 68 there was no opening at the normal anal position, in other words, an imperforate anus. In all but 4 of these 68, we have found an abnormally placed rectal connection or opening, or so-called "fistula." The various positions of these abnormal rectal openings have seemed to fit a pattern. We hope that the presentation of this pattern may be of help to surgeons.

Since many of the congenital defects which come to our attention represent the arrest of an otherwise normal embryologic development, we believe that the study of such embryologic arrests is one source of information which can be applied to the study of human embryology. Another source is, of course, the study of human embryos, and a third is the study of the anatomy of animals lower on the evolutionary scale.

Our deductions from the study of the pattern in our series do not conform entirely to the account of the embryology of the rectum and anus which is ordinarily given. By reviewing our material and, at the same time, going back to descriptions of the human embryo, we have hoped to bring these two sources into agreement.

CLINICAL OBSERVATIONS

In each of the 70 cases to be described the actual pathologic condition of the rectum and anus has been observed by one of us (A.H.B. Jr.). In some cases the patients have been operated on by one of our colleagues, but in these instances we have had the privilege of seeing the patient either before or during surgery. The observations, then, have been of a uniform nature.

In our presentation we plan to dwell chiefly on the group of 68 infants in whom we found no opening at the usual position of the anus (Ladd and Gross, type III). Sixty-four of these were found to have a rectal opening at an abnormal position, such as in the bladder, urethra, vagina, or perineum. There were 4 cases with a blindly ending large bowel, and the findings in each will be described.

In addition to these 68 cases, we have observed 1 instance of supra-anal stenosis (Ladd and Gross, type I), and 1 case of atresia of the rectum in which the rectal ampulla and the anal canal were present beyond the obstruction (Ladd and Gross, type IV). We shall discuss these 2 cases separately.

MALES WITH NO OPENING AT THE NORMAL ANAL POSITION

A summary of our findings can best be shown diagrammatically. Figure 1 shows the approximate positions of the rectal openings found in a group of 33 male infants. In this group there appears to be a fairly even distribution of the abnormal rectal opening from the region of the lower bladder or posterior urethra and then posteriorly along the perineum until the normal position of the anus is reached.

Males with rectourinary connection and imperforate anus. Of our group of males, 10 were known to have a rectourinary connection together with an imperforate anus (Fig. 2). One patient was seen in whom the rectouri-

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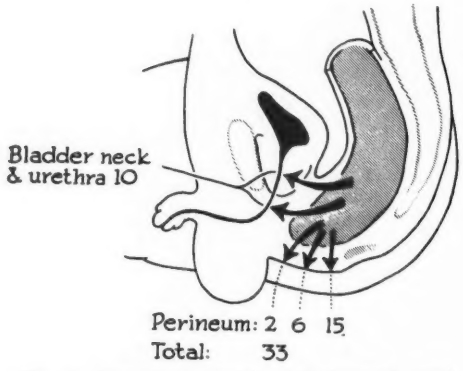

FIG. 1. Approximate positions of abnormal rectal openings found in 33 male infants with imperforate anus. Note distribution of positions of openings suggesting an embryologic failure of "migration."

nary opening was patent until the age of 7 years, although during infancy the pouch of the rectum had been anastomosed to the skin of the perineum at the anal dimple. This opening was proved by cystoscopy to be just distal to the bladder neck. Eight others were found to have a patent rectourinary opening by the presence of meconium in the urine, and at operation. The exact levels of the openings into the urinary tract could not always be accurately identified, but they were known to be either very low on the posterior aspect of the bladder or else at some point in the proximal urethra.

In 1 case the rectum ended in the shape of a cone, or the tip of a horn, with the apex directly at the mucosa of the proximal urethra. Whether or not this connection contained a small lumen could not be determined with certainty. It seems probable to us that it did.

Males with rectoperineal opening and imperforate anus. Of the male infants without an opening at the normal position of the anus, 23 were seen with a rectal opening somewhere between the normal anal position and the scrotum. An example of these is shown in the accompanying photograph (Fig. 3). Fifteen of these 23 were within the posterior one-third of the space between the normal position of the anus and the base of the scrotum. Six were in the middle one-third; and 2 were in the anterior one-third. In each of these, the normal position of the anus was judged by the presence of deeper pigmentation of the skin and the fact that this area could be made to pucker by pricking the buttock with a pin. We have taken this reaction to mean that the sphincter ani externus lies at this position beneath the discolored skin.

Curiously, 9 of these 23 babies showed a longitudinal band of tissue running from the normal anal position over the anteriorly placed rectal opening (Fig. 4). This has been called a congenital median band by

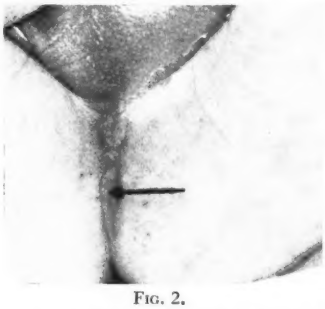

FIG. 2.

FIG. 2. Perineum of male infant with no anal opening. The area at the point of the arrow demonstrates a puckering on stimulation. At surgical operation an opening was demonstrated from the tip of the rectum into the posterior urethra.

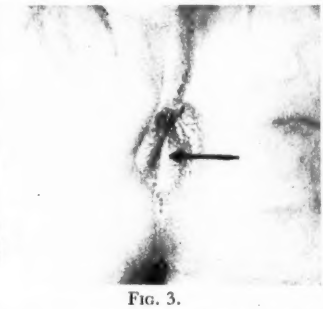

FIG. 3.

FIG. 3. Anteriorly placed rectal opening in male infant. External sphincter at arrow.

FIG. 4.

FIG. 4. Anteriorly placed rectal opening in male infant, with "congenital median band" extending across it. External sphincter beneath point of arrow.

Felix and by us (1). Several other patients have shown a midline ridge over the normal position of the anus. We have thought that such abnormal midline tissue is related to the anterior closure of the anal tubercles as they swing together in the midline and when the single band of tissue formed by this juncture has not joined smoothly with the tissue of the lateral perineum. The others did not show this band when first seen by us.

It was our impression 4 years ago that a congenital median band could occur across a normally placed anal opening (1). We now believe that if such a band is present, the rectal opening is most likely to be anterior to the external sphincter muscles.

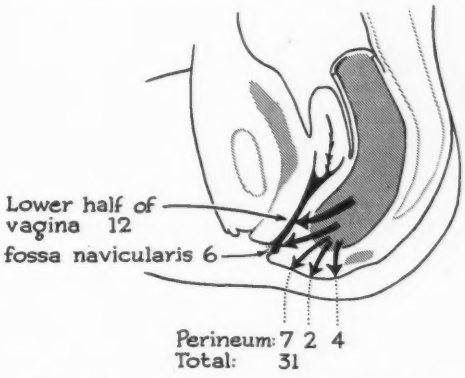

FIG. 5. Approximate positions of abnormal rectal openings found in 31 female infants with imperforate anus. Distribution from lower vagina downward and posteriorly suggests an embryologic failure of "migration."

FEMALES WITH NO OPENING AT THE NORMAL ANAL POSITION

Figure 5 shows diagrammatically a series of 31 cases in which we have seen an abnormal rectal opening in the female. Again we see what appears to be an orderly distribution of the rectal openings starting in the posterior vaginal wall, then down its posterior wall to the fossa navicularis and backward across the perineum until the normal anal position is reached.

Females with rectovaginal opening and imperforate anus. Eighteen of our female patients were described as having a rectovaginal fistula. The level of the opening in the vagina was difficult to determine at surgery because of the extremely small size of the vaginal aperture. However, 6 of these were placed at the outlet of the vagina in the fossa navicularis, or fourchette. The remaining 12 were at varying positions on the posterior vaginal wall, and we have the impression that all of these were in the lower portion of the vagina. One opening was found in one lumen of a double vagina. One was associated with exstrophy of the bladder.

Abnormal rectoperineal opening in the female with imperforate anus. Thirteen of our female patients with imperforate anus showed a rectal opening in the perineum between the usual anal position and the vulva (Fig. 6). Four of these openings were in the posterior one-third of the perineal area between the anal dimple and the posterior vulva. Two were in the middle one-third, and 7 in the anterior one-third. One of these infants also had a congenital median band.

It will be seen that in none of our female patients was there a connection between the bowel and the urinary tract.

INFANTS WITH NO OPENING AT THE ANUS, WITH BOWEL ENDING BLINDLY

In the following 4 cases no opening was found at the anus, and yet the large bowel ended blindly within the peritoneum with no rectourinary nor rectovaginal opening.

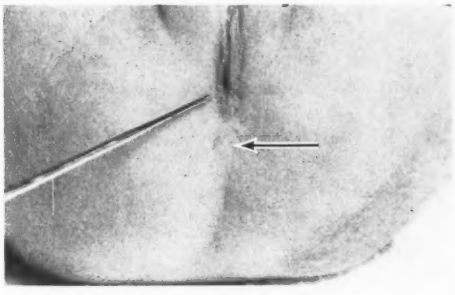

FIG. 6. Anteriorly placed rectal opening in perineum of female infant, indicated by tip of probe. Position of external sphincter at point of arrow.

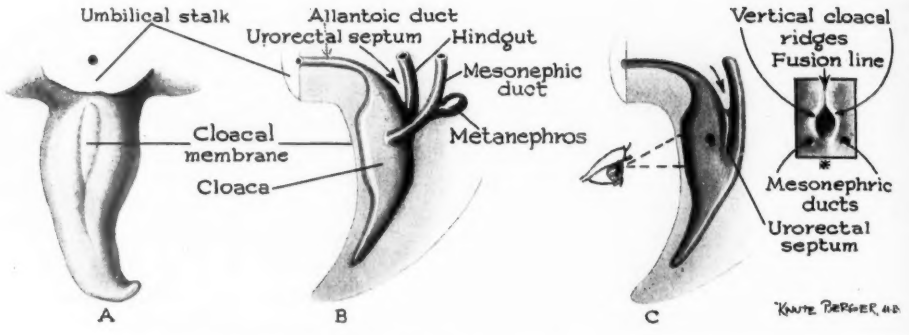

FIG. 7. A, External view of ventral surface of tail of 5 millimeter embryo to show cloacal membrane covering cloaca. B, Lateral view of 5 millimeter embryo to show hindgut entering cloaca. C, Medial view of wall of cloaca, and anterior view of posterior wall of cloaca to show fusion lines between cloaca and hindgut. Also shown are cloacal ridges which later come together to divide cloaca into rectum and urogenital sinus.

These represent exceptions to our cases of imperforate anus with an abnormal connection elsewhere:

CASE 1. Baby boy S., a newborn infant was first seen in 1955. This baby had a large and edematous penis and a flaccid perineum in which no anal reflex could be obtained. Physical examination and roentgenograms showed absence of the sacrum and coccyx. The baby died and, at autopsy, was found to have a completely blind large bowel ending at the upper pelvis. There was no connection with the urinary tract. In addition there was a congenital atresia of the proximal urethra with enormous dilatation of the bladder and marked bilateral hydronephrosis. The bony sacrum and coccyx were missing and, with them, the normal nerve supply from this region.

CASE 2. D. H., a female infant, was first seen in 1955 at the age of 1 day. Externally there was no opening posterior to the vulva. On surgical exploration this baby was found to have multiple abnormalities in the pelvic viscera. The distal colon ended blindly at about the level of the brim of the pelvis. There was a bicornate uterus with its two portions connected with the back of the bladder, with a fallopian tube and ovary attached to each uterus. In addition, the baby had a horseshoe kidney with obstruction of the left ureter. She had no sacral abnormalities.

CASE 3. D. A., a male infant, was first seen at the age of 2 days, in December 1956. Externally there was found to be a distended abdomen. The perineum showed a marked dimple at the normal position of the anus. This dimple was seen to pucker strongly when stimulated. At operation he was found to have the patent portion of the intestinal tract terminate at the dilated cecum which lacked firm lateral peritoneal attachments. In the left lower quadrant we found an isolated segment of large bowel in the shape of the sigmoid, 2 inches in length, and attached to the posterior peritoneum. This had a very small diameter and was blind at each end, with the lower end at about the brim of the pelvis. There was a tiny isolated portion of large bowel, also blind at each end, in the pelvis beneath the peritoneal floor.

CASE 4. S. M., a 2 day old female infant, was seen in 1954. This baby was found to have no external opening posterior to the vulva. A combined abdominoperineal operation demonstrated a blind large intestine with its distal end at the level of the pelvic brim. Extending caudalward from the blind bowel into the pelvis was a series of cysts containing clear mucus. There was no connection between the bowel lumen and the vagina. This infant subsequently died of cyanotic heart disease.

EMBRYOLOGY

All events of significance in the formation of separate urogenital and rectal tracts and the development of normal external genitalia and normal anus occur roughly between the fourth embryonic week and the sixth fetal month. This is during the period of growth from 4 to 200 millimeters respectively of crown-rump length. At about the 6 millimeter stage the urorectal septum has formed as a coronally placed partition in the cloaca, thus dividing it into ventral and dorsal parts, or the urogenital sinus and the rectum respectively (Fig. 8A). This separation of

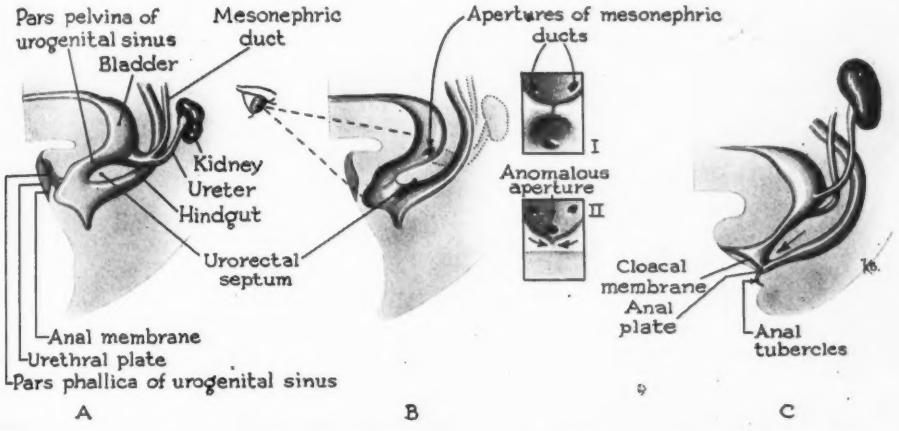

FIG. 8. A, Lateral view of hindgut and urogenital sinus in 8 to 9 millimeter embryo. This shows further downward displacement of end of hindgut as it is moved downward by growth of urorectal septum. B, Medial view of hindgut and urogenital sinus in 8 to 9 millimeter embryo. Inset I, Posterior wall of junction of urogenital sinus and hindgut. Inset II, Posterior wall of junction of urogenital sinus and hindgut in hypothetical case in which the "migration" of the rectum has stopped on the posterior wall of the urogenital sinus. This leaves rectal opening close to mesonephritic duct openings and subsequently into bladder neck or urethra. C, Further descent of rectal opening beneath cloacal and anal membranes. Rectal opening now at site of future fossa navicularis.

the urogenital from the rectal tracts is, however, not as simple as the foregoing statement would imply. A rectal aperture into the cloaca existed initially and the seeming descent of the urorectal septum makes this aperture appear to descend steadily lower in the posterior part of the cloaca (Fig. 7B and C) until finally the rectal aperture is brought to the perineal area (Fig. 9B) where it is prevented from showing externally by that portion of the cloacal membrane known as the anal plate (Fig. 9A). This formation of the urorectal septum, or the "descent" of the aperture which this septum partially surrounds may be thought of as a "migration of the rectal opening" in the posterior part of the cloaca—a migration which progresses caudalward until the aperture reaches the perineum. This manner of expressing the events as a "migration" was initially suggested in a more limited way by Sir Arthur Keith.

During the time of the descent of the urorectal, or cloacal, septum there is a medialward bulging of ridges on the right and left cloacal walls occurring synchronously with the descent of the septum (Fig. 7C). In fact, the septum is really being formed by the midline fusion of these longitudinal ridges (Fig. 7C). Thus a curving or arching septum is descending from above like a curtain being pulled downward at the same time that an extension from each of the lateral walls is moving medialward. The extension toward the midline of the lateral cloacal ridges may be likened to the bilateral narrowing of the aperture on a fluoroscope screen. As Retterer first pointed out, it is the fusion in the median plane of the right and left linear ridges which really forms the septum. If, at any time during this phase, the arching roof of the aperture failed to descend further (i.e., midline fusion fails to occur), the extensions coming in from the sides could still unite in the midline below this unexpected aperture, thus leaving an anomalous connection between the rectum and the urogenital sinus. In such an embryo

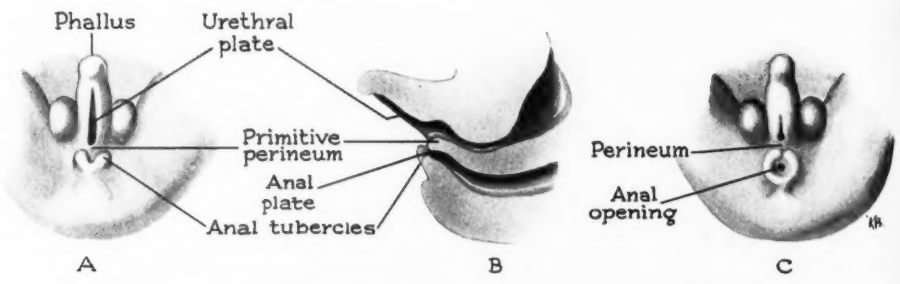

FIG. 9. A, External view of 19 millimeter male embryo in which the anal membrane remains over the rectal opening as it has been moved back almost to the anal tubercles. B, Medial view of "A." C, External view of further stage in male embryo. Anal plate has disintegrated to reveal rectal aperture back at normal position, within the encircling anal tubercles.

the perineum could be completed in the usual fashion except that the rectal extremity would not be carried to the proper site for the perineal aperture to develop as a normal anus. Since the anal orifice itself, as a muscular and cutaneous structure, arises as a separate entity by the ring-like fusion of right and left anal tubercles, it could still develop in a rudimentary fashion in its expected place in spite of the absence of a rectal canal leading into it.

The urogenital sinus now formed as the anterior division of the cloaca is essentially a tube which may be divided into three parts known from above downward as the pars vesica, the pars pelvina, and the pars phallica (Fig. 8A and B). The pars vesica is the precursor of part of the bladder in both male and female embryos. The pars pelvina becomes the prostatic and membranous urethra in the male and the entire urethra in the female. The pars phallica contributes to the formation of the penile urethra in the male and to the lower one-third of the vagina and the vestibule in the female. The upper portion (probably two-thirds) of the vagina has an origin from the fused lower ends of the müllerian ducts which come to be interposed between the urogenital sinus and the rectum. At this point it should be pointed out that some embryologists have contended that the whole of the vagina is derived from the paired müllerian ducts (or the uterovaginal canal), while others have claimed that the entire vagina is derived from the sinovaginal bulbs which, in turn, arise from the urogenital sinus epithelium. A more moderate view is expressed by those who believe that the lower part of the vagina only is of sinovaginal bulb origin. This lower part is variously claimed to be the lower one-fifth or lower one-third. The origin of the vagina is germane to our discussion because it is easy to understand the development of the rectovaginal fistula when we consider that the lower one-third or possibly all of the vagina may be derived from tissue (sinovaginal bulbs) which arose from the epithelium of the posterior wall of the urogenital sinus. On the other hand, we would be at a loss for an embryologic explanation of the rectovaginal fistula if the origin of the vagina is entirely from the lower end of the fused müllerian ducts, since at no time in embryonic life is there a connection between the müllerian ducts and the rectum.

In the male embryo a failure of adequate caudal migration of the rectal aperture down the posterior wall of the cloaca would lead to a connection between the pars pelvina of the urorectal sinus and the rectum. Since the pars pelvina gives rise to the prostatic and membranous portions of the urethra, the so-called rectourethral fistula of a malformed baby would open into this posterior portion of the urethra.

In the female embryo an equivalent failure of adequate caudalward migration of the rectal opening (i.e., the retention of an anomalous communication between the urogenital sinus and the rectum) would result in a communication with structures derived from the pars pelvina and the posterior part of the pars phallica of the urogenital sinus (Fig. 10A and B). Such structures are the inferior one-third (or all) of the vagina and the portion of the vestibule between the vaginal aperture and the posterior commissure of the labia minora. This latter commissure is also called the fourchette (Fig. 8C). Thus, the lower end of the rectum in the female may open anomalously into the lower part of the vagina or into that part of the vestibule between the introitus and the fourchette. Essentially this is the fossa navicularis of the adult woman, an area commonly miscalled the fourchette.

Ectopic anal apertures into the male perineum at some point anterior to the normal site of the anus are due to failure of adequate caudalward migration of the rectal extremity so as to be able to meet the site of the developing anus at the anal tubercles in spite of the fact that the descent of the urorectal septum was completed (Fig. 8B, II). Sufficient mesoderm must grow into the lower part of the urorectal septum and the midpart of the cloacal membrane to be able to develop the perineal tissues dividing the anus from the urogenital structures (perineal body of adult), and thus displacing the rectal aperture posteriorward, to thereby place the anus at its definitive site in the perineum. Figures 7A, 9A, and 9C portray these sequential changes in the formation of the perineal body as seen from the surface view.

Ectopic anal apertures into the perineum in the female behind the posterior commissure of the labia majora, but anterior to the normal site of the anal aperture, will also be devoid of a proper sphincter ani externus and, as in the male, represent the result of a defective alignment between the perineal extremity of the rectum and the anal tubercles (Fig. 8C).

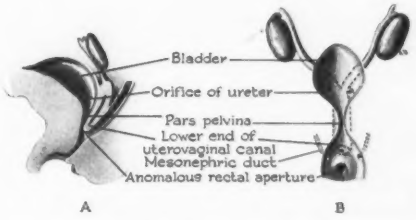

FIG. 10. A, Lateral view of 22 millimeter female embryo to show hypothetical anomalous rectal opening "trapped" in pars phallica of urogenital sinus. This would persist at birth as a rectovaginal opening with no opening at the normal position for the anus. B, Frontal view of "A."

DISCUSSION

As patients with imperforate anus receive more attention, and as studies of the pathology of this condition are published, it is noticeable that an increasing proportion of the patients are described as having a fistula, or, as we prefer to put it, an ectopic rectal opening, to either the urinary tract in the male or to the vagina in the female, or to the perineum in either sex.

Of those who have in recent years reported a large series of infants with imperforate anus, Potts and associates, Gross, Moore and Lawrence, Santulli, Lee, Lu, and Nuboer and Aken have all emphasized the fact that one must be prepared to find an abnormal connection between the rectal pouch and the genitourinary tract, the vagina, or the perineum. In each of their series, relatively large proportions of the infants were known definitely to have had such an abnormal connection. Of our own group, in 64 cases out of 68 such a connection was found. The other 4 seem to have been different entities.

When an ectopic opening is present and yet goes unrecognized, and the rectum is brought down to the normal anal position without dividing the original opening into the urinary tract in the male or the vagina in the female, the results leave a good deal to be desired. We have seen this happen on several occasions, and believe that it has come about through lack of realization on

the part of the surgeon that a rectal opening into the male urinary tract or into the vagina in the female is virtually always present. In our experience such an opening may be very minute and, in fact, practically microscopic, especially in the males, yet we believe that it must be found and closed by mobilizing the rectal portion downward to form the new opening at the position of the sphincter ani externus.

No discussion of abnormalities of the rectum and anus would be complete without reference to the classification proposed by Ladd and Gross in 1934. This classification has been used extensively by recent authors, and it serves an excellent purpose in allowing uniformity of reporting cases.

Of type I, we have seen but 1 case which seems to fit the criteria of stenosis of the rectum which they have outlined. This occurred in a 13 months old boy who was found to have a stenosis above the anal canal. This baby had always been constipated. Dilatations were performed with satisfactory improvement. We wonder whether some of the cases included in this group by Ladd and Gross would not now fall into the diagnosis of Hirschsprung's disease. Their original diagrams show the stenosis fairly high in the rectum. These diagrams resemble some of the roentgenograms which we see in patients whom we now know to have Hirschsprung's disease. In 1934, when the classification was originally proposed, the pathology of Hirschsprung's disease was not generally understood.

As regards Ladd and Gross's classification, type II, in which a membrane covering the anus is described, the closest to this which we have observed has been the congenital median band. This may be the anomaly to which they refer. Indeed, we have found 10 of these in our relatively small group. Denis Browne in England has stated that he has never encountered an anal membrane pure and simple in what must be a very large experience.

We entertained the possibility that a thin membrane covering the anus might be perforated by the physician who originally attended the newborn infant and that such an entity therefore might not come to the attention of a surgeon. To explore this possibility we questioned 5 of our obstetric colleagues with a combined experience of approximately 43,500 deliveries in private practice. We selected these particular men because each is a good observer and each enjoys a reputation for intelligent and diligent interest in the welfare of the infants whom he delivers. Although each of these men had seen various other types of rectal abnormalities, not one could recall having seen a membrane overlying the anal aperture. These facts make us think that the so-called anal membrane must be an extremely rare condition.

Our experience with type III, which includes 68 cases, has been reviewed in the foregoing.

We have treated 1 child with type IV abnormality. This boy was first seen by us at the age of 6 years. He had a transverse colostomy which had been created at birth. We found him to have a normal appearing anal canal extending up into a rectal ampulla which was approximately 1 inch in depth. At operation the proximal blind end of rectum was found to terminate in the pelvis in direct contact with the pouch of the ampulla. One could postulate that this case represents an atresia of the rectum with a cause similar to the atresias seen higher in the intestinal tract.

We can do no more than conjecture as to the cause of the 4 type III cases in which the large bowel ended blindly within the peritoneum. Two of these (Boy A and Girl M) could probably be best considered multiple atresias of the colon. In each of the other 2 (Girl H and Boy S) multiple abnormalities were demonstrated in the region of the pelvis. These could conceivably have been caused by a local somite defect as suggested by Stephens.

If our findings and embryologic deductions have any merit, they will be as an exposition of the fact that in the absence of a

normal opening at the anus, one *must* expect an ectopic opening from the distal rectum into the urinary tract in the male, or the vagina in the female, or in the perineum in either sex. The few exceptions can be readily identified at surgical exploration.

SUMMARY

A study of the local pathologic conditions present in 70 cases of abnormalities of the rectum and anus is presented.

In 68 cases there was no rectal opening at the normal position for the anus. In 64 of these an opening was demonstrated from the tip of the rectum into the lower bladder or posterior urethra in the male, or into the lower vagina in the female, or else anteriorly placed in the perineum in either sex. In only 4 cases with no opening at the normal anal position did the large bowel end blindly.

In 2 cases an anal opening was present at the usual site, with a supra-anal stenosis being present in one, and an atresia of the rectum in the other.

Studies of the embryologic source material and deductions from our own material suggest that the rectal opening normally "migrates" as an almost separate entity caudalward during the formation of the septum which divides the cloaca into the urogenital system and the rectum. When the rectal opening reaches the level of the developing perineum it appears to be moved posteriorly to its normal position where it becomes encircled by the separately formed sphincter ani externus.

When this "migration" is arrested and the rectal opening does not reach the normal position of the anus, one should expect to find the rectal opening somewhere along its course.

The concept of "incomplete migration" of the rectal opening is suggested as the probable cause in the majority of cases of imperforate anus.

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MULTICENTRIC CARCINOMAS OF THE ORAL CAVITY

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THE CONCEPT of epithelial carcinoma originating from a single minute focus at a single instant in time has been seriously challenged in recent years. The frequently observed gross multiplicity of epithelial carcinomas such as those of the skin, urinary tract, or gastrointestinal tract, as well as significant microscopic observations by Willis, Slaughter, and Collins and Gall has led to the concept of multicentric origin of epithelial carcinoma. This concept is perhaps best expressed as follows in the words of Willis: "In human as in experimental carcinogenesis the effective stimuli are applied, not to one cell or one small group of cells, but to a more or less extensive area of epithelial tissue. All the epithelium in that area is acted upon similarly, though of course usually not equally. Neoplasia will commence where stimuli have been maximal, but the neoplastic response will later be manifested by neighboring tissue that was subjected to the same original stimuli."

Many of the basic observations underlying the concept of multicentric origin of epithelial malignancy have been made in the study of carcinoma of the oral cavity. Here the lesions are readily accessible to direct observation, and the relationship of possible carcinogenic influences and premalignant lesions to the ensuing carcinoma is frequently quite clear cut.

Sarasin was probably the first to publish a detailed study of this problem when in 1933 he presented 30 cases of nonsimultaneous multiple epitheliomas of the oral cavity. Later in that same year, after a statistical study of 1,548 cases of carcinoma of the buccal cavity (including the lips), Lund concluded that the incidence of second primary lesions in the buccal cavity was approximately 15 times greater than that expected by chance alone. In 1946 after a study of 80 patients with intraoral carcinoma, Slaughter found that 14 patients or 18 per cent had grossly apparent multicentric lesions. In 1952 Byars and Anderson reviewed 166 cases of cancer of the oral cavity and, after excluding contiguous lesions and multicentric lesions in a single area of leucoplakia, they still found that 20 patients, or 12 per cent, had multiple oral cancers. In 1957 Wilkins and Vogler reported that of 81 patients with gingival cancer, a total of 17 or 21 per cent had multiple lesions of the oral cavity (14 had multiple simultaneous cancers; 3 had multiple nonsimultaneous cancers). Evidence that this tendency to multicentricity may also extend to include the epithelium of the pharynx, larynx, and esophagus has been presented in studies of Scheel, Engelbreth-Holm, and Videbaek.

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SELECTION OF CASES

Cases for the present study were selected from the files of the Mayo Clinic covering the 10 year period from January 1, 1944, to December 31, 1953. The pathologic findings were reviewed in all cases of carcinoma of the oral cavity proved by examination of surgical specimens obtained during this period. The clinical, surgical, and pathologic records were reviewed in all cases in which 2 or more specimens had been submitted and proved malignant by pathologic examination. Cases were included in the present study as multiple simultaneous carcinomas if the patient presented 2 or more discrete lesions clearly separated by intervals of normal mucosa. Cases were included as multiple nonsimultaneous cancers only if the most recent lesion was clearly separated from the site of excision of the initial lesion, regardless of the time intervening between

diagnosis of the two lesions. All cases were discarded in which any reasonable doubt existed that one of the lesions may have represented a recurrence, local extension, or metastasis from a single primary focus.

OBSERVATIONS

During the 10 year period of this study, a total of 732 patients (578 males; 154 females) were found at the Mayo Clinic to have pathologically confirmed squamous cell carcinomas of the oral cavity, that is, fauces, palate, tongue, gingivae, and buccal surfaces. Of this group, a total of 64 patients (55 males; 9 females) were demonstrated to have multiple discrete carcinomas of the oral cavity—a rate of occurrence of 8.7 per cent. All lesions were squamous cell carcinomas. Of the 64 patients 21 had simultaneous lesions and 43 had lesions occurring at intervals ranging from 1 to 25 years, the average interval being 7.1 years.

The frequency of occurrence of leucoplakia in association with multicentric oral cancer was noted by Sarasin as 67 per cent in the patients of his study. Wilkins and Vogler reported the incidence of associated leucoplakia in their patients with multiple oral cancers to be 79 per cent, whereas it was only 40 per cent in their entire series of patients with gingival cancer. A comparably high association of this premalignant condition also was noted in this study—48 of the 64 patients in this series were observed to have leucoplakia demonstrated either by clinical or pathologic examination.

Sarasin also suggested syphilis and tobacco as possible etiologic factors in the patients in his series (Fig. 1). In the present study, the histories or serologic studies for 5 patients, or 7.8 per cent, gave evidence of previous syphilitic infection. A definite history of the use of, or abstinence from, tobacco was obtained from 49 of the male patients in this study. Of this group, 46, or 94 per cent, were using or had used tobacco in some form. It is of interest that 22, or 48 per cent, of those using tobacco either smoked cigars or chewed, thus repeatedly bathing the mouth

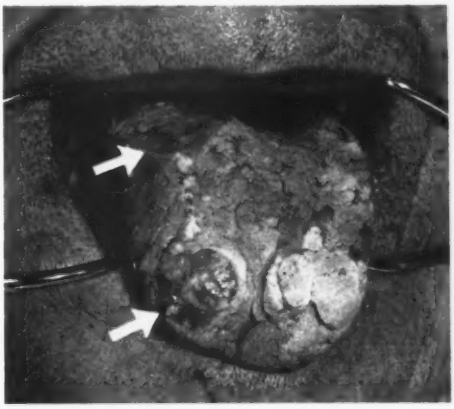

FIG. 1. Multiple carcinomas on a tongue with extensive leucoplakia. The results of serologic tests were positive (positive Kline, Kahn, Hinton, and Kolmer tests) and the patient gave a history of heavy smoking.

in tobacco juices. This relationship was brought out strikingly in one elderly gentleman who had chewed for his entire adult life and habitually pouched his chaw in his right cheek. When seen at the clinic, the entire right buccal surface, and only the right buccal surface, was the site of extensive leucoplakia and 2 discrete squamous cell carcinomas. Wilkins and Vogler reported a similar disproportion in tobacco habits in their series of patients with gingival cancer —57 per cent of all their male patients who used tobacco either chewed tobacco cuttings or snuff. It would be presumptuous to state that the evidence presented in this study and the others quoted constitutes statistically valid proof that tobacco is an etiologic factor in the production of oral cancer; however, the inference is so strong that it can hardly be ignored. It is the responsibility of the physician to interdict firmly the use of tobacco in any form by all patients treated for oral cancer or with premalignant leucoplakia.

That the tendency to multicentricity in oral carcinoma is not limited to the oral cavity alone but extends to the contiguous squamous cell mucous membrane is evidenced by the fact that an additional 55 pa-

tients with oral cancer had associated epitheliomas of the lips, pharynx, larynx, or esophagus. The over-all occurrence rate of multicentric cancer for the 732 patients in this group is thus raised to 16.4 per cent.

COMMENT

Whereas the occurrence of grossly apparent multicentric lesions in this series and in the literature is substantial, still more impressive is the histologic study of Slaughter. By careful examination of 14 operative specimens of oral carcinoma, he found 13 of the 14 to show definite microscopic evidence of multicentricity. He further concluded that many so-called recurrences may in reality be new foci of cancer arising in the peripheral field of a previously treated epithelioma.

Lund stated that in the patient with known oral cancer, even when no premalignant lesion such as leucoplakia is visible, the entire buccal mucosa must be considered in a premalignant condition. With this possibility in mind, any physician who assumes the responsibility of caring for these patients also must assume the responsibility of insisting on frequent and regular follow-up examinations. In addition, Sarasin has suggested the following steps as positive measures in preventing the development of a second cancer which might well be reemphasized here: (1) eradicate leucoplakia, (2) stop the use of tobacco, (3) eliminate alveolar-dental infection, and (4) correct defective dental prosthetic devices.

SUMMARY

Of 732 patients with proved oral cancer seen at the Mayo Clinic during the 10 year period from 1944 through 1953, a total of 64, or 8.7 per cent, were found to have 2 or more discrete oral cancers.

Associated leucoplakia was found in 75 per cent of the patients with multiple oral lesions. An overwhelming majority of the patients were users of tobacco, particularly in the forms which expose the mouth to tobacco juices.

The tendency to multicentricity shown by patients with oral cancer also extends to involve the contiguous squamous epithelium of the lips, pharynx, larynx, and esophagus. Fifty-five patients with oral carcinoma were found to have additional primary lesions in these locations, thus raising the over-all occurrence rate of multicentricity to 16.4 per cent.

When oral cancer develops, all of the contiguous squamous mucous membrane must be considered as highly susceptible to future malignant change. It is the responsibility of the physician to insist on frequent and regular follow-up examinations so that any second lesion may be detected and treated in its early stages. It is also his responsibility to initiate appropriate prophylactic measures to eliminate any possible sources of carcinogenic irritation to these regions.

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LESIONS OF THE SALIVARY GLANDS

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THE SALIVARY GLANDS may be grouped into major salivary glands and minor salivary glands. The minor salivary glands are found diffusely in the region of the mouth, pharynx, and orbit. Thus such salivary tissue is found in the lips, tongue, floor of mouth, pillars of fauces, hard and soft palate, and lacrimal glands. This tissue is subject to the same lesions as the major salivary tissue, but disease in it is rare and it is not the intention to discuss it in any detail as it presents no special problem in therapy.

This discussion is concentrated on the major salivary glands, viz., the parotid, the submaxillary, and the sublingual salivary glands. Of these three, the sublingual gland rarely gives rise to trouble, and when it does it presents no particular problems in therapy because its removal is not especially difficult. It does not appear to be subject to inflammations. Perhaps this is due to the fact that it does not have one duct but several, and therefore obstruction or stricture of one will have but minor effect upon the whole gland. One lesion which does occur in this region, and which may be due to a blocked duct of a sublingual gland, is a ranula. However, the origin of this lesion is by no means accepted as the sublingual gland. The sublingual gland is subject to tumor formation, and mixed salivary tumor does occur in it rarely but very much less frequently than in the parotid gland. It is therefore not proposed to discuss the sublingual gland in further detail.

The submaxillary gland is subject to both inflammatory lesions and tumor formation. Of these two conditions inflammation is the more frequent and is commonly associated with stone formation. It is interesting to note that the submaxillary gland has the longest duct of the three major salivary glands and that it is subject to calculous disease more frequently than either the parotid gland or the sublingual gland. Indeed, from the surgeon's point of view the submaxillary gland is chiefly of interest because of calculus formation, whereas the parotid gland is chiefly of interest because of tumor.

The submaxillary gland does not present a problem surgically, and little attention is given to it because it is readily excised without harm to the patient. Removal is purely an anatomic exercise.

The picture is very different when one turns to the parotid. This gland has been the subject of much attention in the literature. The reason is that the major pathologic condition found is tumor formation of interesting characteristics. Both the benign and the malignant varieties of tumor are pleomorphic, the histologic appearances are of consuming interest, and both have a distressing habit of recurring. The usually quoted figure for recurrence of benign mixed parotid tumors is 20 to 25 per cent. The fact that the figures from the Saskatoon Cancer Clinic records show a remarkably low recurrence rate, viz., 6 per cent for these benign mixed tumors, is one reason for this communication.

The peculiar aspects of neoplasms of the parotid gland would, however, not have aroused so much surgical interest if the gland could have been as readily excised with as little disability to the patient as

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TABLE I.—TUMORS OF SALIVARY GLAND TISSUE

	No.	*Per cent Incidence*	*Per cent Recurrence*
Benign			
Mixed tumor	79	61.2	6.5
Adenolymphoma	6	4.4	nil
Malignant			
Mixed tumor	17	34.6	35.0
Carcinoma	27		
Total	129		

the submaxillary gland. The intimate association of the facial nerve with the parotid gland is the cause of the difficulty. Certain other structures pass through the gland, viz., the auriculotemporal nerve and the internal maxillary artery. Both of these structures may be sacrificed with impunity, but sacrifice of the facial nerve produces a severe deformity due to asymmetry of the face. One of the worst features is the patient's inability to close the eyelid. Ectropion results, and this produces epiphora. It is fear of damaging the facial nerve which has rendered surgeons diffident in the adequate treatment of parotid gland tumors. As a result inadequate incisions are used, inadequate removal of the tumor is done, and recurrence is frequent.

There are three types of lesions of the salivary glands to be considered: (1) benign or malignant neoplasms, (2) traumatic lesions, and (3) inflammatory lesions. It is proposed to concentrate mainly on the topic of neoplasms. Furthermore, it is not intended to deal with neoplasms which are not peculiar to the salivary tissue, viz., hemangiomas, fibromas, or lipomas, which may be found in any part of the body.

The neoplasms to be dealt with are as follows: benign, viz., mixed salivary tumors and adenolymphomas, and malignant, viz., mixed salivary tumors, mucoepidermoid carcinoma, adenocarcinoma, and squamous cell carcinoma.

MATERIAL

All lesions of the salivary gland (155 in all) seen from 1932 to 1956 in the Saskatoon Cancer Clinic were reviewed. One hundred and twenty-nine were neoplasms and 26 were miscellaneous conditions. The pathologic slides of 148 of the cases were reviewed and checked. Seven cases were not available for checking, and these were all in the malignant neoplasm group and involved the parotid gland. Table I sets out the broad distribution of the neoplasms of those 129 cases together with over-all recurrence rates. Table II describes the classification and distribution of the miscellaneous group of lesions. The neoplasms have been grouped according to the classification of Foote and Frazell, of the New York Memorial Center for Cancer and Allied Diseases. The 7 cases, in which the slides were not available for checking, had been diagnosed as follows: malignant mixed tumor in 1, mucoepidermoid carcinoma in 1, squamous cell carcinoma in 2, adenocarcinoma in 1, and undesignated carcinoma in 2 cases.

TABLE II.—MISCELLANEOUS LESIONS

Diagnosis	*No.*	*Site*	*Sex*	*Age, yrs.*	*Treatment*
			M4		Radiation for 2
Chronic inflammation	6	Parotid	F2	15-73	Surg. exc. for 4
Sialitis	3	Submaxillary	F	59-66	Surg. excision
Gland cyst	1	Sublingual	M	27	Surg. excision
Duct cyst	2	Parotid	F	13, 34	Surg. excision
Abscess cavity	1	Sublingual	F	34	Drainage, antibiotics for Staph. aureus
Tuberculosis	1	Sublingual	M	18	Exc. of mass of gland
Actinomycosis	1	Parotid	M	54	300 r. for 3 days, sulfa. and penicillin
Calculi	5	Submaxillary, 3 in duct, 2 in gland	M	35-61	Surg. excision
Branchiogenic cyst	2	Parotid	M	23, 52	Surg. excision
Chronic granuloma	1	Parotid	M	45	Biopsy
Chronic lymphadenitis	1	Sublingual	M	61	Exc. of gland
Lipoma	2	Parotid	M	38, 42	Surg. excision
Total	26				

The 26 miscellaneous cases are of interest insofar as they represent a differential diagnosis problem in swellings of the salivary gland areas. It will be seen that 5 lesions have nothing to do with salivary gland tissue other than fortuitous propinquity, viz., lipoma in 2, chronic lymphadenitis in 1, and branchiogenic cysts in 2 cases. Five cases of salivary calculi were found, all involving the submaxillary gland. Three cysts were found—1 involved the sublingual gland and the other 2 involved Stensen's duct. There were 13 cases of chronic inflammation, 11 of which were nonspecific. There was 1 case of tuberculosis of the sublingual gland and 1 case of actinomycosis of the parotid gland.

The neoplasms consisted of two groups: benign, 85 and malignant, 44 cases. The benign group consisted of 79 benign mixed tumors and 6 adenolymphomas.

TABLE III.—TUMOR DISTRIBUTION

Tumor	*Parotid*	*Submaxillary*	*Sublingual*	*Ectopic*	*Total*	*Per cent*
Benign mixed	72	2		5	79	61
Malignant mixed	11+(1)*	5			17	
Mucoepidermoid carcinoma	4+(1)*				5	
Squamous cell carcinoma	4+(2)*				6	
Adenocarcinoma						34
Adenoid cystic	4	1			5	
Trabecular	1	1			2	
Mucous cell		1			1	
Acinic cell		1			1	
Unspecified	2+(3)*	1		1	7	
Adenolymphoma	6				6	5
Totals	111	12	0	6	129	100

*Tissue slides not available for recheck.

BENIGN TUMORS

Adenolymphoma. The adenolymphoma is known as papillary cystadenoma lymphomatosum by the Armed Forces Institute of Pathology and by other writers as Warthin's tumor, cystic papillary adenoma, or oncocytoma. Histologically these tumors are distinctive. They are predominantly found in males and present the classical appearance clinically of a benign mixed parotid tumor. They are benign and do not recur when completely excised.

Benign mixed tumors. These tumors have both epithelial and connective tissue elements in them and hence the word "mixed" is used from a descriptive point of view only. Many synonyms are used, of which pleomorphic adenoma adopted by Eddy is perhaps the best. They represent the commonest tumor of the salivary gland. As noted in Table III, 72 were in the parotid gland, 2 in the submaxillary, and 5 were in sites other than the major salivary glands, viz. cheek, lip, and palate. There was none in the sublingual gland. The origin of these tumors is disputed but the purely epithelial theory is the favorite one at present, it being considered that they arise from adult glandular epithelium. Histologically their most characteristic feature, both primary and recurrent, is their pleomorphism. The characteristic history is that of a painless lump in the region of the lower pole of the parotid gland. The growth pattern is variable. Usually it is slow, but it may be intermittent, and occasionally it is rapid, thereby resembling a malignant tumor. The age of onset of the patients in this series was from 4 to 79 years with an average age of 40 to 50 years. This observation accords well with all other series and is in contrast with malignant tumors, which usually occur in the age range of 50 to 60 years. Females (47) predominated over males (32), which fact is in agreement with other series. Patients delayed coming to their doctor from 1 week to 40 years. The interval between the visit to the family doctor and arrival at the Cancer Clinic varied from 1 day to 15 years. Hence it can be seen that these 79 cases represent a typical series of benign mixed salivary gland tumors. Twenty-six of these 79 patients had had prior treatment before coming to the Cancer Clinic—25 had undergone some form of local excision and 1 had received "several courses of radiation." In 9 of these 25 patients local excision had been performed less than 6 weeks before admission to the clinic, and each of these 9 was im-

TABLE IV.—BENIGN MIXED SALIVARY GLAND TUMORS

	Total No.	*Recurrences*	
		No.	*Per cent*
Primary cases	62	2	3
"Secondary" cases	17	3	18
Total cases	79	5	6

TABLE V.—RESULTS OF TREATMENT OF BENIGN MIXED SALIVARY TUMORS, 1932 TO 1953

Total No.	79*
No. treated in clinic more than 5 yrs. ago	39
No. well at 5 yrs. after admission to clinic	38†
Per cent well at 5 yrs. and free of recurrence	97

*Sixty-two of these patients were previously untreated upon admission to the clinic. Nine of these had a local excision less than 6 weeks prior to admission. The remaining 17 were all recurrent on admission having been treated previously elsewhere.

†The patient who was not well at 5 years died 1 year after admission to the clinic—condition of primary not stated and cause of death unknown. Eight years prior to admission to the clinic he had had an excision.

mediately treated with postoperative x-ray therapy. For the purpose of this discussion, we consider primary or previously untreated cases to consist of those patients who have had no treatment prior to admission to the Clinic, or those who had surgical excision within 6 weeks of admission and were given radiation when first seen. Therefore, there are available 62 primary cases. The remaining 17 patients were all referred with recurrent disease. The results of treatment in the clinic are summarized in Table IV.

It is evident that treatment of recurrent tumors as compared with that of previously untreated tumors increases the chance of yet further recurrence.

TABLE VI.—BENIGN MIXED SALIVARY TUMORS IN 26 PATIENTS ADMITTED TO CLINIC MORE THAN 5 YEARS AGO AND "PREVIOUSLY UNTREATED"

Type of treatment	*No.*	*Result*
Local excision only	10	10 well at 5 years. None have had recurrences
Local excision and radiation	15	15 well at 5 years 1 recurred at 3 years, treated by further excision and well at 6 years
Radiation only	1	1 well at 5 years. Recurred at 7 years, excised and well 12 years later
Total	26	All free of tumor at present time

"Previously untreated" includes those patients who had had an excision within 6 weeks of admission to clinic and had postoperative radiation treatment on admission.

*One of these patients had a "radical resection."

Table IV gives a false picture because it does not take into consideration the length of time since treatment was given. Therefore, an arbitrary figure of 5 years has been taken to study the recurrence rate. It is recognized that these tumors may recur up to 47 years after treatment (McFarland), but the majority recur within 5 years. The results of treatment studied with this 5 year yardstick are set out in Table V.

Details of treatment. The details of the type of treatment, the time of recurrence, and the condition at the end of 5 years in primary cases are set out in Table VI. In Table VII the details of secondary cases are given, i.e., patients treated before they attended the Clinic and who came because of recurrence.

It is of interest to compare these figures with other series. Foote and Frazell report that in their hospital the recurrence rate is 4 per cent or 6 out of 142 cases of "primary" benign mixed tumors followed up for 5 to 15 years. On the other hand, in "secondary" cases the recurrence rate was 28 per cent of 62 cases followed up for 5 to 15 years, which makes an over-all recurrence rate of 12 per cent. The average recurrence rate quoted in the literature is in the realm of 20 per cent. Table VIII sets forth a few of the recurrence rate figures from the literature. In recording recurrence rates it has been pointed out by many investigators that recurrences may occur many years after the original treatment. McFarland quotes a case which recurred 47 years after first treatment, and Kirklin and associates showed that whereas 6.4 per cent recurrences had occurred within 3 years 22.5 per cent of recurrences had occurred after 20 years. On the other hand, Rawson and associates report that local recurrence reaches a peak about 1 year after the initial treatment. McCune, however, states that most recurrences do not appear for from 3 to 7 years. From this discussion it is evident that no mixed parotid tumor can be considered cured.

In reviewing the present series of cases from the Saskatoon Cancer Clinic, it is of

interest to try to explain the low recurrence rate. The first obvious factor is that many of the patients have not been followed up long enough. Thus 74 have had no recurrence but, of these, 34 only have been followed up for 5 years or more. The type of surgery carried out cannot be a factor because the operations were performed by a wide variety of surgeons and no particular type of operation was uniformly used.

The majority of the tumors were excised locally with a small margin of normal gland, or else were enucleated without any margin of normal gland. As Janes has pointed out, this type of excision is now considered inadequate as it is likely that tumor tissue will be left behind. Few surgeons used the classical operation of Bailey or Janes, in which the facial nerve is displayed. The only other factor which can be considered is the irradiation.

In the majority of our cases, viz., 50 out of 62 primary cases, irradiation was administered; in 49, surgical excision plus irradiation was used.

Much disagreement exists as to whether radiation therapy should be used in association with surgical excision. Ahlbom is strongly in favor of the combined attack on these lesions and calls the treatment radiosurgery. He states that out of 85 benign parotid mixed tumors so treated 5 recurred and responded to further irradiation. On the other hand, Eddey is equally definite that radiation has no place in their treatment. He claims no recurrence in a series of benign mixed tumors treated by surgery alone from 6 months to 10 years ago.

Radiation technique and policy. Only 1 course of treatment is given and the dosage is uninfluenced by the type of surgery done. Usually external irradiation is prescribed using a single field of a size varying from 5 by 5 centimeters to 10 by 10 centimeters depending on the extent of the tumor. A common field is 6 by 8 centimeters. With 200 to 400 kilovolt x-rays the dosage varies from 4,500 to 5,000 roentgens in about 20 days to 5,500 to 6,000 roentgens in 32 days, the actual dose depending on the size of the field used. With radioactive cobalt telecurietherapy the dosage is approximately 10 per cent higher. Treatments are equal and daily. Usually the skin reaction does not progress beyond a brisk erythema. A mucositis of the pharynx is produced, with loss of taste, dryness of the mouth, and sometimes dysphagia. All of these symptoms are transitory. There has been no necrosis or late reaction.

In some cases, when a tumor of the parotid is confined to the flat preauricular area and does not appear to extend deeply, posterior to the ascending ramus of the mandible, a single plane radium implant is performed, either at the time of the excision or 10 days later, the former being preferable. There is no interference with the healing of the wound. The area implanted is approxi-

TABLE VII.—BENIGN MIXED SALIVARY TUMORS IN 13 PREVIOUSLY TREATED PATIENTS ADMITTED MORE THAN 5 YEARS AGO

Type of treatment	*No.*	*Results*
Local excision only	3	1 well 6 years 1 recurrent at 5 years (Died intercurrent 6 years) 1 recurrent at 4 years, alive with recurrence at 9 years
Local excision and radiation	8	8 well at 5 years, or longer. None have had recurrence
Radiation only	2	1 well at 20 years 1 died with recurrence at 1 year
Total	13	10 free of tumor at present time 1 died with recurrence at 1 year 1 died with recurrence at 6 years 1 alive with recurrence at 9 years

All patients had recurrent tumors on admission.

TABLE VIII.—QUOTED RECURRENCE RATES FOR BENIGN MIXED PAROTID TUMORS

	Year	*Per cent recurrence*
Sistrunk	1921	18.3
Stein and Geschickter	1934	20.0
McFarland	1936	34.2
Marshall and Miles	1947	15.0
Rawson, Howard, Royster, and Horn	1950	31.0
Benedict and Meigs	1930	42.5
Jerome	1954	14.5
Ahlbom	1935	9.0
Smiddy	1956	30.0
Eddey	1957	nil
Janes	1957	6.0

TABLE IX.—BENIGN MIXED TUMORS TREATED BY SURGERY ALONE

History No.	*Site*	*Weight of tumor, gm.*	*Previous treatment*	*Clinic treatment*	*Result*
			GROUP 1		
5488	Parotid		Removed 10 yrs. previously	Local excision	Recurred 3 mos. later. Refused further treatment. Died 6 yrs. later—cardiac
6320	Parotid		Removed 8 yrs. previously	Multiple recurrence removed again	Known to have recurrence 4 yrs. later (patient's report). Large recurrence 10 yrs. later (doctor's report)
13609	Parotid		Removed 5 yrs. previously. (Also previous radon)	Enucleated	Well 6 yrs.
19883	Parotid	4.5	Removed 18 yrs. previously	Recurrence—enucleated	Well 3 yrs.
4068	Palate		Original diagnosis—lymphosarcoma. Treated with x-ray without response	Excision 10 yrs. later	Well 15 mos.
			GROUP 2		
5016	Parotid	3		Enucleation	Well 11 yrs.
6562	Parotid			Enucleation	Well 10 yrs.
12597	Parotid	8		Enucleation	Well 6 yrs.
14091	Parotid			Radical excision of large tumor parotid. Did not return for x-ray	Well 6 yrs.
13125	Parotid			Excision	Well 6 yrs.
13305	Parotid	11		Enucleation	Well 5 yrs.
16319	Parotid			Tumor bulging into pharynx. Removed through mouth	Well 5 yrs.
16202	Parotid			Large tumor. Enucleation. Refused x-ray	Well 5 yrs.
15917	Parotid	1.5		Biopsied. Subsequent resection. No residual tumor therefore no treatment	Well 5 yrs.
9351	Parotid. Swelling soft palate and pharynx			Tumor removed through mouth	Well 5 yrs.
21314	Hard palate			Small tumor. Biopsied only. Refused further treatment	Well 2 yrs.
25727	Inner aspect of cheek	0.5		Excisional biopsy	Too early for assessment

Group 1—Previously treated; recurrent when first seen.
Group 2—Previously untreated.

mately 6 by 6 centimeters and a dose of 6,000 roentgens in 170 to 200 hours at ½ centimeter from the plane is prescribed. There is no reaction to this treatment except a brisk erythema of the skin which sometimes proceeds to moist desquamation.

Benign mixed salivary tumors have been treated in three ways by surgery alone, surgery and irradiation, and radiation alone. These three methods will now be reviewed in detail.

Surgery only. The results of surgery alone are set out in Table IX. They are divided into two groups: (1) previously treated cases recurrent when first seen and (2) previously untreated cases.

In group 1 there were 5 recurrent cases, 2 of which recurred after radiation treat-

ment, 1 in which no recurrence had developed after 6 years, and 2 of which have been followed up less than 5 years, so that in only 1 out of 3 can the result be stated to be satisfactory at the present time. Three of 5 may ultimately prove to be satisfactory according to the 5 year follow-up yardstick.

Group 2 is the more interesting. It consists of those patients who had had no previous treatment and who were treated by surgery alone. There were 12 of these cases and to date there are no recurrences, so that on these grounds local surgery alone in primary cases would appear to be very satisfactory. But on more careful analysis of these cases certain facts emerge. One patient had adequate surgical excision according to modern opinion, with exposure of the facial nerve. This patient has been well 6 years. Three patients had enucleation only without exposure of the facial nerve and these have been well from 6 to 11 years. One patient had an excisional biopsy. A further local excision was carried out within 3 weeks and no tumor tissue was found. This patient has been well 5 years. In essence, this surgery was anatomically adequate to deal with the very small tumor. In 1 case the tumor was situated at the lower pole of the superficial lobe of the parotid gland hanging down like a teardrop. It was possible to remove it completely with an adequate margin of normal parotid tissue without disturbing the facial nerve. This patient has been well 5 years. In 2 cases removal was through the mouth from the deep lobe of the parotid gland. These patients have been well 5 years and presumably an adequate margin of gland was removed with the tumor. In the remaining 4 cases the tumors were all in ectopic positions, 1 on the inside of the cheek and 2 in the palate. Here complete excision of all salivary tissue in the area could unquestionably be achieved.

Therefore, to summarize, only 8 of these previously untreated tumors were in the parotid. Three of them were known to have been adequately removed and 2 were from the deep lobe of the parotid gland which leaves 3 cases of classical parotid tumors removed by a very localized excision. Results in these have been satisfactory so far.

TABLE X.—MALIGNANT SALIVARY TUMORS

	Parotid	*Submaxillary*	*Sublingual*	*Ectopic*	*Total*
Malignant Mixed	12	5			17
Mucoepidermoid Carcinoma	5				5
Squamous cell Carcinoma	6				6
Adenocarcinoma	10	5		1	16
Total	33	10		1	44

These figures, therefore, do not constitute an argument in favor of the use of local surgery alone in all previously untreated cases of benign mixed parotid tumors.

Surgery and radiation. The cases listed under "surgery and radiation" are difficult to evaluate from the point of view of the effectiveness of x-ray treatment. Excision must have been incomplete in many cases. The excellent results following local excision (usually enucleation) followed by radiation are possible evidence of the value of radiation (See Tables VI and VII.)

As previously described, the radiation treatment used was usually x-ray or radioactive cobalt telecurietherapy, but occasionally radium implantation immediately following excision was employed for some parotid tumors. Nine patients were treated with radium implant all being well after a period of from 3 to 10 years. There was no sequela.

Three cases, all tumors of the parotid, recurred after surgery and external radiation:

1. 17796—Co^{60}, 5,000 r. in 3 weeks; recurred in 10 months. Well 4 years following further local excision.
2. 17119—Recurrence case. Co^{60}, 5,500 r. in 23 days (6 × 8 cm.). Recurred in 1 year. Well 2 years following local excision.
3. 7697—200 Kv., 5,000 r. in 17 days. Recurred in 3 years. Well 6 years following local excision.

Thus all patients treated by surgery and radiation are well at the present time.

In series taken from the literature comparable to this series, in which similar sur-

TABLE XI.—FIVE YEAR SURVIVAL IN CASES OF MALIGNANT TUMORS OF THE SALIVARY GLANDS

Type	*Total No. 1932 to 1955*	*No. treated over 5 years ago*×	*No. of 5 year survivors*	*Per cent 5 year survivors*
Malignant mixed	17*	11*	9*	82
Adenocarcinoma	14*	10*	4	40
Mucoepidermoid	5*	4*	3*	75
Squamous cell	6*	4*	3*	75
Adenocarcinoma	2*	2**	1*	50
All cases	44	31	20	65

×Date taken from admission to Clinic or Clinic treatment, whichever was later.
*Unchecked slides in 1 of these cases.
**Unchecked slides in 2 of these cases.
It should be noted that these figures include previously treated patients admitted to the Clinic. See Table XII for previously untreated cases.

TABLE XII.—FIVE YEAR SURVIVAL IN CASES OF MALIGNANT TUMORS OF THE SALIVARY GLANDS PREVIOUSLY UNTREATED

Type	*No.*	*No. surviving 5 years after treatment*	*Per cent 5 year survivors*
Malignant mixed	9	9	100
Adenocarcinoma	7	3	43
Mucoepidermoid	3	2	66
Squamous cell	4	3	75
Unclassified carcinoma	1	0	0
Total	24	17	71

"Previously untreated" cases include those patients who, before coming to the Clinic have had a biopsy only, or who, within 6 weeks of being admitted to the Clinic, have had a surgical excision which has been followed immediately by radiation treatment in the Clinic.

gery was used alone without radiation, recurrence rates of 20 to 25 per cent are reported. Therefore, the addition of radiation seems to have been helpful in reducing the recurrence rate to an over-all figure of 6 per cent.

Radiation only. The following are the details of the cases of patients treated by radiation alone:

1. 1668—X-ray only, 2,700 r. in 18 days. Recurred 7 years later. This recurrence was excised and the patient is well 12 years later.
2. 1706—Recurrent. Treated by x-ray 3,270 r. in 11 days. Died in 1 year—cause unknown. State of parotid area at death unknown.
3. 1169—Recurrent. Treated with x-ray and radon seeds. Necroses occurred but healed spontaneously. Well 20 years later.
4. 19336—Recurrent after 3 excisions. Treated with Co^{60}, 5,500 r. in 20 days. Well 4 years later.

In 2 of these cases (3 and 4) there was complete resolution with x-ray treatment only. In the first case (1) there was resolution for 7 years followed by recurrence, but the dosage was grossly inadequate. The effect in the fourth case (2) was unknown. These few cases suggest that radiation has some effect on these tumors.

Comment. Certain conclusions may be drawn from these data, always allowing for the fact that the follow-up has still been inadequate in length of time. Undoubtedly a 20 year follow-up is needed in mixed salivary tumors. (1) Local surgery and postoperative radiation give excellent results without sequelae. (2) Radiation alone is shown to have a curative effect in some cases. (3) Local surgery alone in previously untreated cases was successful in the few cases in which it was undertaken in the present series, but only 3 out of 8 of these cases fell into the usual categories of typical mixed parotid tumors. (4) Local surgery alone was not satisfactory in the treatment of recurrent cases. (5) Local surgery plus radiation was successful in the treatment of patients admitted with recurrent disease.

MALIGNANT NEOPLASMS

Forty-four charts were reviewed, but in only 37 cases were slides available for classification. Table X sets out this classification in the four broad categories. It will be noted that there were 17 malignant mixed salivary tumors and 27 carcinomas. It is also interesting to note that 5 of the malignant mixed tumors occurred in the submaxillary gland out of a total of 17 such tumors. Equally interesting is the fact that of these 5 tumors 4 recurred. By comparison, only 2 of 79 benign mixed tumors occurred in the submaxillary gland. No malignant mixed tumors occurred in the ectopic glands. The sex incidence was 28 males to 16 females, which is the reverse ratio of that for benign tumors. The average age of the patients with malignant tumors was 10 years older than of those with benign tumors.

The 5 year survival results of treatment of malignant salivary tumors are presented according to the type of tumor (Table XI). The over-all 5 year survival rate is 65 per cent, comparing favorably with a report by

TABLE XIII.—TYPE OF TREATMENT FOR MALIGNANT TUMORS OF THE SALIVARY GLANDS IN PATIENTS UNTREATED PRIOR TO ADMISSION TO THE CLINIC

Type	*No.*	*Treatment*	*Result at 5 years or more*
Malignant mixed	8	Local excision and radiation	8 Well at 5 years. None had a local recurrence but 1 had a resection of a secondary in the lung 5 years ago and is now well. 1 died after 5 years—lung secondaries
	1	X-ray treatment only	1 Well at 10 years
Adenocarcinoma	4	Local excision and radiation	1 Well at 5 years—No recurrence 1 Dead at 4 years—Local recurrence and distant metastases 1 Dead at 7 months—Primary well, distant metastases 1 Dead at 6 years—Locally recurrent and distant metastases
	2	Local excision only	1 Well at 6½ years—But has had 2 recurrences in interval 1 Dead at 6 years—Locally recurrent and distant metastases
	1	Radiation only	1 Dead at 1 year—Intercurrent disease, primary well
Mucoepidermoid	1	Radiation and local excision	1 Well at 8 years—No recurrence
	1	Radiation and radical excision	1 Well at 5 years—No recurrence
	1	"Radical" surgery	1 Dead at 2 years—Intercurrent disease, primary well
Squamous cell	4	Local excision and radiation	1 Well at 5 years—No recurrence 1 Dead at 10 years—Intercurrent disease, primary well but had had a recurrence 1 year after treated—treated by excision 1 Dead at 9 years—Primary well, intercurrent disease 1 Dead at 14 months—Recurrent
Unclassified cancer	1	Radiation	1 Dead at 1 year—Cause unknown and state of primary unknown

Ariel, Jerome, and Pack of 32.3 per cent in patients with carcinoma of the parotid gland free of disease at 5 years.

Table XII gives 71 per cent as the 5 year survival rate in patients with malignant tumors previously untreated when admitted to the Cancer Clinic, demonstrating the well known fact that once a carcinoma has recurred the prognosis is much worse, and that the first treatment is of the utmost importance.

These two tables (XI and XII) also show that the prognosis is best for malignant mixed tumors and squamous cell carcinomas. Conversely, the prognosis is poorest for adenocarcinoma. Another point not brought out in the tables is that 3 of the 10 patients with submaxillary gland carcinoma died of widespread metastases, 2 of the 10 are alive but have had pulmonary metastases, and a further 1 had local recurrence. Thus, only 4 of the patients with submaxillary carcinoma are free of recurrence, and of these 1 died of intercurrent disease after 2½ years, 1 was treated only 8 months ago, and one 4 years ago. This finding would suggest that the prognosis in carcinoma of the submaxillary gland is rather poor which is surprising in view of the fact that the whole gland can be readily removed. It would suggest that a more radical clearance of the anterior triangle of the neck should be essayed in this type of case.

Details of treatment. The types of treatment given in the series of malignant tumors are presented in Table XIII. It will be seen that the primary treatment in 18 of the 24 cases was a combination of surgery (usually local) and radiation. In 3 cases radiation only was used, and in 3 others surgery only.

TABLE XIV.—EVIDENCE OF EFFECTIVENESS OF RADIATION IN MALIGNANT PAROTID TUMORS

	Treatment	*Result*
Malignant mixed		
6693	Treated 400 Kv., 6,000 r. in 32 days	Well 10 years
7506	Incomplete excision. Treated 200 Kv., 7 cm. diameter circular field; 5,300 r. in 17 days	Well 8 years
17414	Recurrent after local excision, 5 months prior to coming to the clinic. Treated Co^{60}, 10 cm. × 8 cm.; 5,000 r. in 22 days	Well 2½ years. Died intercurrent disease 2½ years
15483	Incomplete excision followed by 8 cm. diameter circular field; 200 Kv., 5,000 r. in 18 days	Well 5 years
Adenocarcinoma		
8693	400 Kv., 10 cm. × 10 cm. field; 5,000 r. in 21 days	Well 1 year. Died 1 year. Intercurrent disease
Mucoepidermoid		
16921	Incomplete excision 6 weeks prior to Co^{60} 10 cm. × 6 cm. field; 5000 r. in 20 days	Well 5 years
Squamous cell		
21305	Radiation only; 200 Kv., 12 cm. × 8 cm. field; 5,500 r. in 33 days	Well 2½ years later
11623	Radiation only; Co^{60} 7 cm. × 5 cm. field; 7,000 r. in 27 days	Well 2½ years

Evidence of the effectiveness of radiation is hard to get, as most cases were treated by postoperative radiation immediately after local excision and, of course, there is no way of knowing whether the latter was complete or not. The cases mentioned above, however, seem to indicate unequivocally that radiation alone can be curative in some cases of cancer of the salivary glands.

The methods of radiation therapy used in treating malignant salivary tumors are similar to those described for benign mixed salivary tumors except that the dosage is higher, the treatment field larger, and the duration of the treatment somewhat longer. Again only one course of therapy is planned, and x-ray or radioactive cobalt telecurietherapy (usually the former) is employed using a single field, with equal daily doses. The whole gland, or the whole extent of the tumor, whichever is greater in area, including a margin, is covered. No attempt is made to cover the lymph node drainage area, unless nodes are involved and are inoperable. The dosage varies with the size of the field, with the over-all time of treatment and with the type of radiation employed. The general level of skin dose given is 4,500 to 5,500 roentgens in 21 days or 5,000 to 7,000 roentgens in 32 days.

When the tumor is in the parotid and does not appear to extend beneath the ascending ramus of the mandible a single plane radium implant may be performed. In the present series 3 patients were treated in this manner following surgical excision. All are well more than 5 years later. The dosage ½ centimeter from the plane was respectively 6,000 roentgens in 138 hours, 6,000 roentgens in 170 hours, and 6,500 roentgens in 217 hours.

One patient treated in 1932 had x-ray treatment and radon seed implant.

A mucositis of the pharynx or mouth, or both, always occurred, starting about 2 weeks after the initial treatment. Sometimes there was also dysphagia. These symptoms subsided 1 to 3 weeks after the end of treatment. An erythematous skin reaction always developed, progressing frequently to moist desquamation which healed 2 to 4 weeks after the end of treatment.

In only 1 case, treated by x-ray therapy and radon seed implant in 1932, was there necrosis of the mandible. This condition eventually healed and the patient died 9 years later, the primary lesions having healed. There was no other case of necrosis or late reaction, or other complication due to radiation.

Table XIV outlines those cases treated with radiation in which the radiation alone appears to have been successful in eradicating the disease. In other cases in which radiation followed immediately after surgery no conclusions can be drawn as to its efficacy, except from a consideration of the 5 year survival rate, which is very satisfactory.

Of the 24 primary cases treated more

than 5 years ago, surgery alone was performed in only 3. Two of these patients had an adenocarcinoma and recurrence following local excision within 5 years. The third patient had a radical removal of a mucoepidermoid carcinoma, but died after 2 years from cardiac failure, the primary tumor being "cured" at death.

There were 7 other patients treated more than 5 years previously all with recurrent lesions when first seen. In most, palliative treatment only was given and the group is too heterogeneous for analysis.

From these experiences, therefore, one can conclude that in the treatment of malignant salivary tumors: (1) A combination of surgery (even if of a local nature) and postoperative radiation is successful in a large percentage of cases. (2) Radiation alone can be effective in eradicating the disease. (3) Surgery of a local type by itself is likely to be unsuccessful.

GENERAL DISCUSSION OF TREATMENT

Surgical treatment of tumors of the sublingual and submaxillary glands does not present any particular difficulty because these glands can be excised completely without any disability to the patient. Therefore, attention will be concentrated on the parotid gland.

A lump in the parotid gland should be regarded in the same way as a tumor of the breast. It should be excised with normal gland tissue surrounding it, and a frozen section examination carried out. This is contrary to the advice of McFarland who advocates waiting till the tumor is "ripe." Certainly approximately 70 per cent of all parotid tumors are benign but it is impossible to tell whether a tumor is malignant or benign simply on history and physical examination, unless the signs of malignancy are unequivocal. There are no unequivocal signs of benignity. It is therefore important to have a definite plan in handling all parotid tumors.

It is true that the figures presented in this series of 129 salivary tumors show that local excision, or enucleation, plus radiation give good results, but it is claimed that these results would be still better if a more aggressive and a more anatomic type of operation were performed in all these tumors. Few surgeons would be content to remove a carcinoma of the breast locally by enucleation only and then rely on high dosage radiation treatment to deal with any malignant tissue left. Yet with parotid tumors this treatment was frequently carried out, with surprisingly good results. A better surgical method would appear to be that advocated by Janes, viz., wide excision of all parotid tumors with visualization of the facial nerve. If malignancy is found, then total parotidectomy with preservation of the facial nerve should be attempted. Where the authors disagree with Janes is on the question of postoperative irradiation. He advocates irradiation only in the presence of malignancy, if removal has been incomplete, or if there has been spillage of tumor in the wound at the time of removal. We, on the other hand, have produced evidence that radiation is effective in these tumors whether benign or malignant, that it does no harm to the patient and, therefore, should be used as an adjunct to surgery. It is important to realize that parotid tumors are serious lesions, that one-third are malignant, and that they are deceptively easy to remove. They should not be treated lightly.

SUMMARY

One hundred and fifty-five cases of salivary gland lesions seen in the Saskatoon Cancer Clinic from 1932 to 1956 are reviewed. One hundred and twenty-nine were neoplasms. Seventy-nine of these neoplasms were benign mixed tumors.

Recurrence rates and 5 year survival rates in patients free of disease are recorded. Benign mixed salivary tumors have an over-all recurrence rate of 6 per cent. Patients with malignant tumors have an over-all 5 year survival rate of 65 per cent.

In general the treatment was surgery plus postoperative irradiation. The details

of the radiation technique and dosage are stated.

Evidence is produced to show that salivary tumors do respond to adequate radiation and that the best results will be obtained with adequate surgery plus adequate radiation.

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A COMPARISON OF IN VIVO CHANGES FOLLOWING ADMINISTRATION OF STRANGULATION OBSTRUCTION FLUID AND CLOSTRIDIUM WELCHII TOXIN

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THE LUMEN of a strangulated, closed loop of ileum in dogs has been observed to be the site of accumulation of dark, foul fluid. Moreover, after 24 to 30 hours this material passes through the bowel wall into the peritoneal cavity and is toxic when injected into the peritoneal cavity of normal animals (2). If the strangulated loop is placed in a plastic bag so that the animal is not exposed to the fluid, life is indefinitely prolonged. Following perforation of the bag with escape of the fluid into the peritoneal cavity all animals are dead within 4 to 6 hours. The specific component of this fluid which is responsible for its lethal properties has not been determined. Cohn has indicated that the Clostridium welchii is of major importance in the lethal issue of this material. It has also been shown that normal animals which received penicillin at the time of injection of the strangulation obstruction fluid into the peritoneal cavity lived longer than those who were not given antibiotics (1).

The following experiments were conducted to compare certain physiologic changes in 3 groups of animals. The first group received a lethal injection of strangulation obstruction fluid. The second group received an equal dose of strangulation obstruction fluid along with penicillin, while the last group received the alpha toxin of the Clostridium welchii.

Collection and preparation of peritoneal fluid. Five healthy mongrel dogs were anesthetized with intravenous nembutal. By utilizing sterile technique, the terminal ileum was exposed and a 10 centimeter closed loop obstruction was created with umbilical tape ties. All veins supplying this segment of bowel were ligated. The abdominal wound was closed after the loop had been returned to the peritoneal cavity.

These animals lived for 24 to 30 hours. At, or shortly before death the peritoneal cavity was opened for withdrawal of the accumulated fluid. This material was placed in sterile containers and refrigerated until used.

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INTRAPERITONEAL INJECTION OF FLUID

Experimental method. Eight healthy adult mongrel dogs were lightly anesthetized with intravenous nembutal. An intramuscular injection of 600,000 units of penicillin was given to one-half of the animals. A femoral artery was cannulated to facilitate the collection of blood samples. Control specimens were withdrawn immediately after insertion of the cannula. Each animal was then given an intraperitoneal injection of strangulation obstruction fluid in the amount of 4 cubic centimeters per kilogram. Blood samples were collected at 2, 4, 6, and 8 hour intervals after injection of the fluid. Red, white, and differential blood counts were made. The hematocrit was determined by standard methods using the Wintrobe tube. Clotting time values were obtained by placing 1 cubic centimeter of whole blood in each of 3 test tubes. Each tube in succession was gently tilted from side to side until clotting occurred. The clotting time was recorded as that time between the entrance of the blood into the syringe and clot formation in

TABLE I.—EFFECTS OF INTRAPERITONEAL FLUID ON CELLULAR ELEMENTS OF BLOOD

Dog No.	*Time, hours*	*WBC X10³*	*RBC X10⁶*	*Hematocrit*
47	Initial	9.7	3.9	30
	2	2.9	5.0	52
	4	3.2	5.3	53
	6	3.0	6.1	57
	8	3.0	6.4	59
199	Initial	13.8	5.2	47
	2	4.2	6.0	59
	4	4.1	7.4	67
	6	3.4	7.9	69
	8	4.9	8.3	70
201	Initial	13.2	4.7	35
	2	5.7	5.7	43
	4	3.5	6.5	53
	6	4.1	6.7	54
	8	4.7	7.6	62
32	Initial	14.8	5.6	41
	2	5.2	6.7	51
	4	3.6	7.3	62
	6	5.8	7.8	67
	8	DIED		

TABLE II.—MEAN CLOTTING TIME VALUES (MINUTES)

Material given	*Initial*	*2 hrs.*	*4 hrs.*	*6 hrs.*	*8 hrs.*
Raw fluid	10.8	11.0	14.4	15.0	17.4
Raw fluid penicillin	9.6	9.9	9.4	13.3	12.4
Clostridium welchii toxin	10.0	11.0	14.5	14.3	18.0

TABLE III.—PLASMA HEMOGLOBIN AND CLOTTING TIME VALUES FOLLOWING INTRAPERITONEAL INJECTION OF FLUID

Dog No.	*Time, hours*	*Plasma hemoglobin, milligrams per cent*	*Clotting time, minutes*
47	Initial	1.8	6.5
	2	10.7	8.3
	4	20.2	8.9
	6	28.4	5.0
	8	31.0	5.0
199	Initial	4.0	6.1
	2	28.0	7.0
	4	32.7	8.9
	6	72.4	10.0
	8	104.0	12.5
201	Initial	1.1	9.9
	2	5.2	6.7
	4	16.0	11.0
	6	7.6	8.7
	8	8.8	7.1
32	Initial	2.1	9.5
	2	12.8	10.1
	4	17.0	10.0
	6	34.8	9.9
	8	36.0	9.1

TABLE IV.—MEAN WHITE COUNT VALUES (WBC X10³)

Material given	*Initial*	*2 hrs.*	*4 hrs.*	*6 hrs.*	*8 hrs.*
Raw fluid	12.8	4.5	3.8	4.1	4.6
Raw fluid penicillin	12.4	6.7	5.8	5.9	5.6
Clostridium welchii toxin	7.6	9.2	14.8	17.2	20.0

the third tube. Plasma hemoglobin was determined according to the method of Dacie. Sodium and potassium determinations were made of fresh serum by utilizing the flame photometer.

Results. Group I.—A marked drop in the concentration of circulating white blood cells was found in all animals. This change was present as early as 2 hours after injection of the fluid. The differential white blood cell count revealed no significant change in the ratio of lymphocytes and leucocytes. There was a constant and progressive rise in the hematocrit of all animals. The concentration of circulating red blood cells paralleled the hematocrit (Table I). The mean clotting time for this group changed from a control value of 10 minutes to 18 minutes after 8 hours (Table II). There was a progressive increase in the plasma hemoglobin values (Table III). No significant changes in serum sodium and potassium were noted.

Group II.—In these animals a progressive leucopenia was also noted although it was not quite as severe as that seen in the previous group (Table IV). The differential count showed little change during the period of observation. A gradual increase in the hematocrit was noted (Table V). A similar change in the erythrocyte count was also noted. The control clotting time was 9.6 minutes and after 8 hours this value was 12.4 minutes (Table II). A gradual rise in plasma hemoglobin was observed. This value after 8 hours was 19.4 milligrams per cent (Table VI). No change of significant magnitude was noted in sodium and potassium values.

INTRAPERITONEAL INJECTION OF CLOSTRIDIUM WELCHII TOXIN

Experimental method. Four adult mongrel dogs were lightly anesthetized with intravenous nembutal following which a femoral artery was cannulated. Control blood samples were collected. Clostridium welchii (type A) toxin with 200 to 300 minimum lethal doses per cubic centimeter (mouse test) was used. Six cubic centimeters of

TABLE V.—MEAN HEMATOCRIT VALUES

Material given	*Initial*	*2 hrs.*	*4 hrs.*	*6 hrs.*	*8 hrs.*
Raw fluid	38	51	59	61	64
Raw fluid penicillin	33	42	50	48	59
Clostridium welchii toxin	40	47	57	61	53

TABLE VI.—MEAN PLASMA HEMOGLOBIN VALUES (MILLIGRAMS PER CENT)

Material given	*Initial*	*2 hrs.*	*4 hrs.*	*6 hrs.*	*8 hrs.*
Raw fluid	2.2	14.2	21.4	35.8	44.9
Raw fluid penicillin	1.6	5.3	7.2	13.3	19.4
Clostridium welchii toxin	2.5	33.9	72.4	9.30	86.3

this material was suspended in 25 cubic centimeters of isotonic saline and administered to each dog as an intraperitoneal drip during a period of approximately 1 hour. Blood samples were collected at 2, 4, 6, and 8 hour intervals after the drip had been started. Similar blood studies as described for the group who received peritoneal fluid were carried out on these animals.

Results. The mean control white blood cell count increased from 7,600 to 20,000 eight hours after injection of the toxin (Table IV, Table VII). There was little change in the differential white blood count during this period of observation. A gradual progressive increase in the erythrocyte count

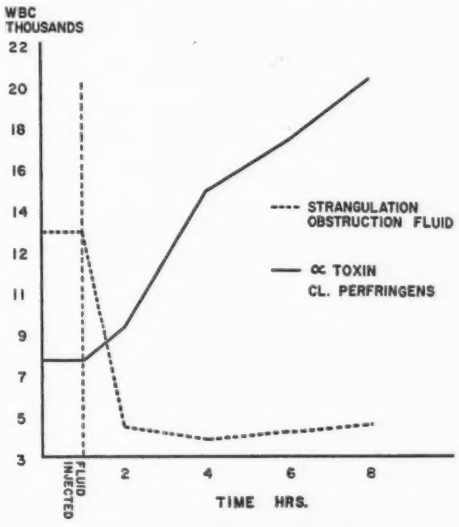

FIG. 1. White blood cell responses following intraperitoneal injection of strangulation obstruction fluid and Clostridium welchii toxin (mean values).

and hematocrit of all animals was noted. The mean plasma hemoglobin increased from a control value of 2.5 to 86.3 milligrams per cent (Tables VI and VIII). The mean clotting time was found to be 10 minutes before injection of the toxin and 18 minutes 8 hours later (Table II). Minimal

TABLE VII.—EFFECTS OF CLOSTRIDIUM WELCHII TOXIN ON CELLULAR ELEMENTS OF BLOOD

Dog No.	*Time, hours*	*WBC X10³*	*RBC X10⁶*	*Hematocrit*
110	Initial	11.1	6.3	47
	2	6.1	6.5	52
	4	9.8	8.2	70
	6	11.3	8.5	74
	8		Died	
120	Initial	9.6	5.5	39
	2	6.8	6.1	47
	4	10.8	7.6	63
	6	13.7	8.6	74
	8	18.1	8.3	71
152	Initial	4.6	4.3	34
	2	9.6	5.9	42
	4	24.5	6.1	47
	6	24.8	6.8	52
	8	22.5	5.3	40
31	Initial	5.0	5.3	46
	2	13.9	5.9	48
	4	14.2	6.0	47
	6	19.0	5.7	47
	8	20.0	6.3	48

TABLE VIII.—PLASMA HEMOGLOBIN AND CLOTTING TIME VALUES FOLLOWING INJECTION OF CLOSTRIDIUM WELCHII TOXIN

Dog No.	*Time, hours*	*Plasma hemoglobin, milligrams per cent*	*Clotting time, minutes*
110	Initial	1.8	9.5
	2	19.3	10.0
	4	49.6	16.5
	6	112.8	14.5
	8	Died	
120	Initial	4.3	11.7
	2	9.8	8.5
	4	26.0	14.0
	6	58.4	14.0
	8	56.0	9.4
152	Initial	2.2	11.2
	2	47.6	13.7
	4	42.4	14.0
	6	——	16.2
	8	——	32.0
31	Initial	1.9	11.0
	2	59.0	12.0
	4	54.0	13.0
	6	41.0	14.2
	8	43.0	12.0

changes in the serum sodium and potassium values were noted.

COMMENTS

The most striking physiologic change in animals receiving a lethal dose of strangulation obstruction fluid was a severe leucopenia. Hill and Stoner have stated that the degree of leucopenic change could be used as an index of the toxicity of strangulation fluid. A decrease in circulating leucocytes was also seen in animals who received penicillin along with strangulation fluid but to a lesser degree. The exact reason why penicillin prolonged the life of these animals was not clear. It seemed improbable that the slight decrease in severity of leucopenic response was the answer. It may be that the circulating antibiotics afforded a degree of protection at a time when the natural body defenses were weakened by the decrease in circulating white blood cells. In none of the animals who received Clostridium welchii toxin was a leucopenia noted. Indeed, quite the reverse was the rule as all animals exhibited a progressive leucocytosis (Fig. 1). If the death of animals who received strangulation obstruction fluid was a result of the marked leucopenia, which was consistently present, then it must be concluded that the toxic nature of this material did not result from the alpha toxin of the Clostridium welchii. This toxin also produced a much greater rise in plasma hemoglobin than did the raw fluid.

CONCLUSIONS

1. A marked leucopenia follows the injection of raw strangulation obstruction fluid into the peritoneal cavity of normal animals.

2. This change is not significantly altered by the administration of penicillin.

3. Prolongation of life in animals which are given strangulation fluid and penicillin may result from temporary protection at a time when natural body defenses are failing.

4. The intraperitoneal injection of Clostridium welchii toxin is followed by a leucocytosis.

5. The rise in plasma hemoglobin level is much greater in animals who receive Clostridium welchii toxin than in those who are given strangulation obstruction fluid.

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THE PATTERN OF WOUND HEALING OF SKIN AUTOGRAFTS AND SKIN HOMOGRAFTS IN THE RAT

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THE MECHANISM of rejection of homografts has been the subject of a voluminous literature. In 1943, Medawar (8) summarized the three main theories proposed until then to explain such rejection as follows: (a) the blood group or natural immunity theory, in which failure of homografts to "take" was attributed to incompatibility of blood groups or to antigen complexes governing tissue compatibility, (b) the cellular theory, in which "individuality differentials" were held responsible for rejection of transplanted tissues, operating mainly through the lymphocyte, and (c) the acquired immunity theory, in which grafted tissues acted as isoantigens calling forth isoantibodies which destroyed them. Since that time, and mainly through Medawar's pioneer efforts, much evidence has accumulated in favor of the acquired immunity hypothesis, and recently it has been presented and discussed at length in a number of conferences to which one should refer for details (2, 12). Although the basic mechanism of rejection may be the same for all homotransplanted tissues, there are differences due to the very nature of the transplanted fragment and of the recipient bed; i.e., the problems of kidney homotransplantation are not the same as those of skin homotransplantation or tumor homotransplantation.

Basically, in a skin graft the aim is wound healing by first intention, since the host's bed is formed by connective tissue from which capillaries and fibroblasts are expected to penetrate into the graft, providing nutrition and adherence. These two phenomena, proliferation of capillaries and formation of fibrous tissue, are essential to the process of wound healing. The vascularization of skin homografts has been studied both experimentally and clinically, and it has been found that penetration of blood vessels with establishment of circulation occurs in the graft quite early and lasts for variable periods of time according to species. Suddenly, however, the blood flow stops completely and the graft is eliminated. Microscopic studies reveal congestion of many capillaries and thrombosis in others, but it is considered that these changes are not the cause but the effect of the death of the graft. On the other hand, the proliferation of connective tissue has received surprisingly little attention, and this is more apparent when one contemplates the great interest that has developed in this tissue in the last decade. In a detailed study of the fate of skin homografts in man, Gibson and Medawar observed that the graft bed differed from that of autografts in the intensity of fibroblastic proliferation and collagen formation. When describing the graft bed of 23 day old homografts they state: "There had been a feeble fibroblast reaction in the graft bed, though not in the granulation tissue on either side, and no new mature collagen fibres were found." The same phenomenon was observed in 31 day old homografts, where as in autografts and in one pair of homografts that had coalesced with each other and looked normal after 31 days, they described the graft bed as follows: "A dense oriented fibroblast reaction was in progress under each graft, and abundant new collagen had been laid down." A similar difference in the graft bed of autografts and homografts was noticed by Medawar (9) in his first experimental study in rabbits, but curiously enough the phenomenon is not dis-

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cussed nor is an attempt made to explain it. In more recent work, experimental as well as clinical, no reference is made to the connective tissue reaction of the graft bed. Engley and associates established a parallelism between the effect of a second wound and a second homograft, but their studies referred to a set of serologic tests performed in the hope of finding humoral changes involved in the process of wound healing. In their own words: "In the two problems, rate of repair of wounds and rate of and reason for sloughing of homografts, there is at least one common question to be resolved. That is whether or not an immune factor or humoral factor is involved which is responsible for initiating or guiding these two processes."

In view of the paucity of data and of the theoretic significance of wound healing in the problem of skin transplantation, it was considered pertinent to examine the mechanism of wound healing during the rejection of homografts. Recently, Dunphy and associates (3, 4, 13) have published a series of studies of wound healing, using histologic, histochemical, biochemical, and tensile strength techniques, and have shown objectively that the use of different methods in the study of a problem will render more complete information than the unilateral approach. Healing involves deposition of ground substance and production of collagen, among other things. Although morphologic and histochemical techniques are adequate for qualitative, and even semiquantitative, observations, it is believed that direct chemical determinations of some of the substances involved in the process of healing will give a more precise picture. Accordingly, advantage has been taken of the fact that the carbohydrate component of the acid mucopolysaccharides of the ground substance of connective tissues is a hexosamine, either N-acetyl-glucosamine or chondrosamine. A biochemical determination of the amount of hexosamines in tissues should correlate rather well with histochemical observations on the ground substance, and this has been found to be true by Dunphy and Udupa (3). Furthermore, collagen and reticulum can be measured by the determination of the amino acid hydroxyproline, which has been shown to be present almost exclusively in the scleroproteins, and at a very high and constant concentration. Therefore, the determination of hydroxyproline in tissues should correlate with histologic observations on collagen and reticulum, and this has also been shown in wound healing by Dunphy and Udupa. Our purpose is to present the results of an experimental study of the mechanism of wound healing in skin homografts performed by histologic and biochemical techniques.

MATERIALS AND METHODS

Forty adult white Wistar rats weighing 200 to 300 grams were used. The animals were kept in pairs and fed a standard mixture, carrots, and water ad libitum. Twenty rats were used for the autotransplants and 20 for the homotransplants.

Surgical techniques. Under ether anesthesia a square piece of skin and subcutaneous tissue, measuring 4 centimeters per side, was obtained from the back of a rat and laid outer surface down on a sterile Petri dish; the subcutaneous tissue was carefully removed from the graft with fine scissors until the fragment was considered to be pure skin. In the case of the autotransplants, the graft was rotated 180 degrees and placed back in its bed; in no case did this procedure take more than 30 minutes. After fixing the extremes of the graft by means of cotton thread, a continuous suture was done and the operative field was protected with a gauze bandage. In the case of the homotransplants, the graft was placed in the back of another rat, previously prepared by taking a similar piece of skin from it. Sutures and bandages were placed as in the autotransplants, and again the whole procedure was carried out in less than half an hour. No antibiotics were used and no animal was infected.

At 2, 4, 6, 8, and 10 days after grafting 2 rats from each group were selected and the transplant and underlying connective tissue

were removed under ether anesthesia. The operative defect was easily closed by sliding the neighboring skin.

Histologic and biochemical studies. The margins of transplant and bed were removed and discarded. The fragment was then divided into 4 long narrow pieces, of which 2 were fixed in 10 per cent formalin, embedded in paraffin, cut at 6 microns and stained with hematoxylin and eosin, Verhoeff-van Gieson, Mallory's aniline blue and Foote's reticulum stains. The other 2 fragments were used for the determination of hexosamines in tissues by the method of Boas, and for the determination of hydroxyproline by the method of Neuman and Logan (10) as modified by Martin and Axelrod.

RESULTS

Gross observations. The course of the transplants was as usual. The autotransplant behaved like a clean, aseptic wound, showing a little edema and reddening of the margins during the first 2 days, and thereafter becoming flattened and more adherent to the underlying bed. At the end of 10 days, every autotransplant had "taken" perfectly well. On the other hand, the homotransplants seemed normal for the first 2 to 4 days, and after that they became elevated over the surrounding skin, dried up, and darkened in color, the margins hardened and separated from the bed and the surrounding skin, and in from 8 to 10 days they were all beginning to slough off.

Microscopic observations. Detailed microscopic observations will not be presented, since with due allowance for differences in methods and in animal species they were quite similar to those published by others. Only brief descriptions are given of the salient features for each of the 5 different dates at which fragments were taken, with special attention to the connective tissue reaction of the graft bed.

Two days. The findings were identical in the autograft and homograft. The line of separation between transplant and bed was clearly seen, and there was slight edema in the connective tissue of the host. There were early signs of capillary dilatation and none of cellular proliferation.

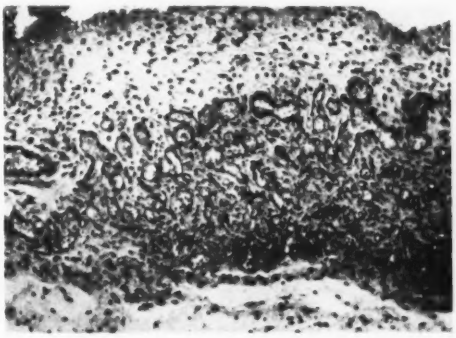

FIG. 1. Photomicrograph of the bed of a skin autograft 4 days after operation. The graft is above and outside the field photographed. There is superficial edema with infiltration by immature fibroblasts, and capillary neoformation and dilatation. Hematoxylin and eosin, ×85.

Four days. At 4 days there was some increase of the edema in the graft bed of the autotransplant, and clear evidence of vascular dilatation and capillary neoformation (Fig. 1). There were many ovoid, plump fibroblasts with vesicular nuclei, forming small groups and without evidence of fibrillogenesis (Fig. 2). The thickness of the vascular and fibroblastic reaction was considerable and the line of separation between graft and bed was still clearly seen (Fig. 3). On the other hand, in the bed of the homotrans-

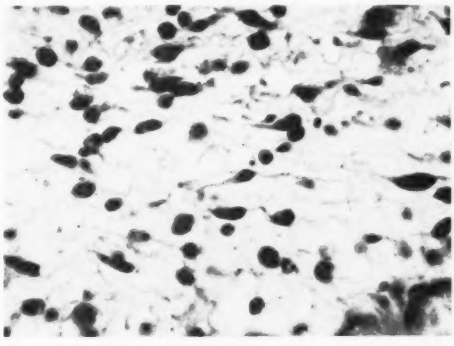

FIG. 2. High power detail of a group of immature fibroblasts seen in Figure 1. Notice the lack of fibrillogenesis. Hematoxylin and eosin, ×320.

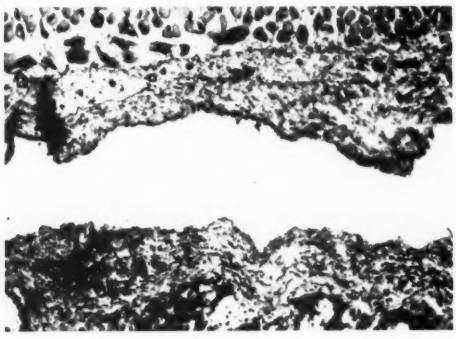

FIG. 3. The line of separation between autograft (in the upper part) and graft bed (lower part). Hematoxylin and eosin, ×70.

plant there were very few fibroblasts. The vascular dilatation was more apparent but the area of reaction was very thin (Fig. 4). The limit between the graft and the bed was clearly seen, and edema was more abundant than at 2 days.

Six days. In the bed of the autotransplant there was considerable progress in the process of wound healing. Edema was important but the capillary neoformation was very apparent, and there was a thick layer of fibroblasts with abundant formation of fibrils, arranged along the lines of stress (Fig. 5). Separation between graft and bed was recognized only in certain areas and it was less apparent than at 4 days. The autotransplant appeared viable and there were only a few lymphocytes between the muscular fibers. In the homograft bed the edema persisted but it was less important, the capillaries were dilated, and the fibroblastic reaction was minimal (Fig. 6). The line of separation between graft and bed was very apparent, and the transplant showed early but clear signs of disintegration with lymphocytic infiltration, necrosis of muscular fibers, and blurring of the limit between epidermis and dermis.

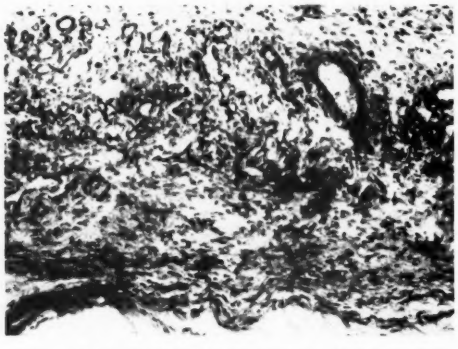

FIG. 4. The bed of a skin homograft 4 days after operation. It can be seen that there is edema, immature fibroblast accumulation, and capillary dilatation, but the reaction is less marked than in Figure 1. Hematoxylin and eosin, ×85.

Eight days. In the autotransplant bed there was complete loss of edema. The limit between graft and bed was not identified; instead, there was a thick layer of connective tissue with a mixture of reticulum and collagen fibers, with predominance of the latter (Fig. 7). Dilated capillaries and plump fibroblasts were still present but scarce. The graft appeared normal. In the homotransplant there was little modification from the picture found at 6 days, except that disintegration of the graft was more advanced.

Ten days. In the bed of the autotransplant there was a decrease in capillaries and immature fibroblasts and there were some hyalinized connective fibers (Fig. 8). The graft was healthy and normal. The homotransplant was almost completely disintegrated and partially eliminated, and it was impossible to recognize it as skin. The bed showed scarce edema and a thin layer of connective tissue with dilated capillaries (Fig. 9). In the lumen of a few blood vessels there were recent thrombi.

Summary of histologic observations. The main differences observed between the autograft bed and the homograft bed were: (a) persistence of edema for a longer period in the homograft bed; (b) a slower fibroblastic reaction in the homograft bed, and (c) a much thinner area of proliferation of connective tissue in the homograft bed.

Biochemical determinations. The results of the determinations of hexosamines in both autotransplants and homotransplants appear in Table I. The results of the quantifications of

FIG. 5.

FIG. 6.

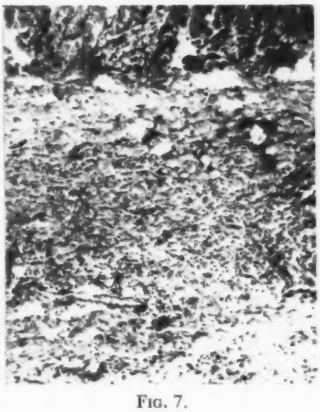

FIG. 7.

FIG. 5. Granulation tissue in the bed of a 6 day old autograft. Hematoxylin and eosin, ×90.

FIG. 6. Edema, very few immature fibroblasts, and some capillary dilatation in the bed of a 6 day old homograft. The line of separation between bed and graft is clearly visible. Hematoxylin and eosin, ×75.

FIG. 7. Fibrous tissue in the bed of an 8 day old autograft. Hematoxylin and eosin, ×90.

hydroxyproline, expressed as collagen according to Neuman and Logan (11), are shown in Table II. These data have been plotted following the pattern established by Dunphy and Udupa (3) in Figures 10 and 11.

DISCUSSION

The results obtained in the autograft experiments are practically the same as those reported by other authors who worked with normal wound healing. The minor differences can be explained by the size of the lesion produced in the rat, which was relatively small in Dunphy and Udupa's experiments and quite large in ours, and by the amount of tissue used for the determinations of hydroxyproline and hexosamine, which was larger in the present work. Disregarding

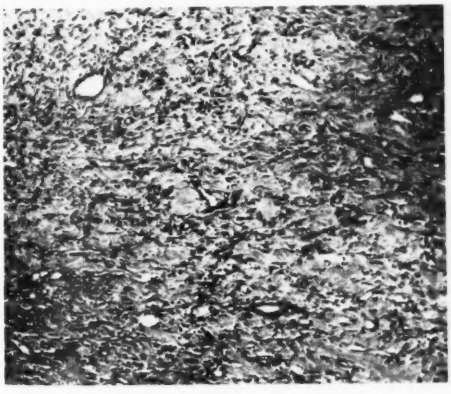

FIG. 8. Photomicrograph of mature connective tissue, showing some hyalinized collagen bundles, in the bed of a 10 day old autotransplant. Hematoxylin and eosin, ×105.

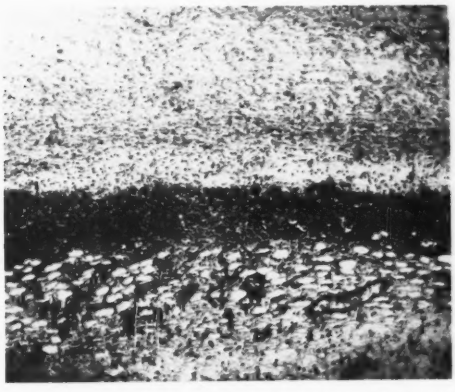

FIG. 9. The area of reaction in the bed of a 10 day old homograft. It is much thinner than in the autograft and it is formed of many immature fibroblasts. There still is considerable edema. Hematoxylin and eosin, ×50.

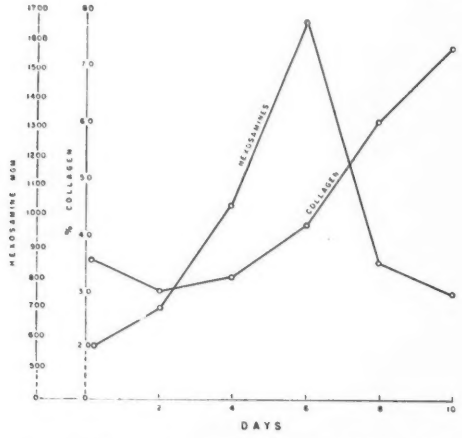

FIG. 10. Pattern of wound healing in autotransplants.

these minor variations the pattern of healing of autografts is, as could be expected, identical to that of closed aseptic wounds, and this identity has been shown grossly, histologically, and biochemically.

On the other hand, the pattern of healing of the homograft bed shows two important deviations from the normal (autograft). First, the figure reached by the concentration of hexosamine is slightly smaller at 6 days, when in both groups of animals this was the day of the highest concentration. Second, although the amount of collagen increases as normal up to the sixth day, after that it shows no further increase, and there is even a suggestion of decrease. These biochemical observations are confirmed by the histologic study in which it was found that both the speed and the size of the fibroblastic reaction were much less pronounced in the bed of the homograft as compared with that of the autograft. Thus, by both histologic and biochemical methods, the observations made by Gibson and Medawar (6) in man, and by Medawar (9) in the rabbit have been confirmed in the rat.

TABLE I.—HEXOSAMINE CONTENT OF AUTOGRAFTS AND HOMOGRAFTS (MILLIGRAMS OF HEXOSAMINE PER 100 GRAMS OF DRY TISSUE

Day	*Autograft*	*Homograft*
2	698	648
4	1021	980
6	1644	1328
8	842	894
10	743	560

In 4 determinations of hexosamine in normal rat skin it was found that the average content was 562 milligrams per 100 grams of dry tissue. Each figure is the average of 4 determinations.

The cause of this disturbance in the normal process of wound healing is not clear. It might be attributed to the mechanical presence of the homograft, but from our studies as well as from those of many others it can be clearly seen that for some time after homotransplantation everything occurs as in the autotransplant, and then something happens which causes the death and rejection of the homograft. Therefore, before the mechanism of rejection has had time to establish itself, the homograft behaves like an autograft, and whatever mechanical influence they have on the bed must be the same for both. Of course, after the emergence of the mechanism of rejection the homograft becomes foreign to the graft bed, and at this moment it might exert some mechanical depression in the process of wound healing. This is the time, however, when collagen proliferation is in process, and it has been repeatedly shown that mechanical influences favor the deposition of collagen. Therefore, we do not believe that the homograft causes any modification in the mechanism of wound healing by mechanical means. It is of interest that the main disturbance of wound healing occurs at the time when rejection of the homograft becomes visible. Before the sixth day after grafting the biochemical pattern is almost normal and the histologic differences in the graft bed are relatively unimportant. This might mean that the mechanism of rejection of the graft is also interfering with normal deposition of collagen, but further speculation is not warranted without additional facts.

One very interesting and unexpected finding in these experiments was the individual behavior of the curves of hexosamine and collagen in the bed of the homograft. In normal wound healing, during the early stages of repair, as well as in our experiments with

autografts, there is a rapid increase in the concentration of hexosamine, reaching its maximum 3 to 6 days after injury, and after that there is a rapid fall to normal or preinjury concentrations. At the time when the concentration of hexosamine begins to fall there is a rise in the amount of collagen, and the inverse relationship which exists between hexosamine concentration and collagen formation has led Dunphy and Udupa to suggest that the early period of healing should be regarded as a productive or substrate phase of repair, instead of a lag period. During this productive phase mucoproteins, sugars, and the soluble precursors of collagen appear in the wound, and there seems to be some evidence that glycine and proline, which constitute two of the important amino acids involved in collagen formation, are present in large quantities in the productive phase. This inverse relationship between hexosamines and collagen has been fortified by the results of experiments in wound healing under abnormal conditions, such as protein deficiency and ascorbic acid deficiency, where there is a delay or lack of formation of collagen with failure of the concentration of hexosamine to fall. Although not on a biochemical basis, the pattern of rise and fall of mucopolysaccharides has been known for some time in wound healing, and there have been some suggestions that mucopolysaccharides play some role in the formation of collagen fibers. It is highly probable that fibroblasts are responsible for both phases of wound healing; i.e., they produce at least a portion of the metachromatic, acid-mucopolysaccharide-protein complex that accumulates in the wound during the first days, and their presence is necessary for the formation of collagen fibers which appear a few days later. If this is true, then the results of the present experiments can be interpreted as suggesting that the mechanism of rejection of the skin homograft interferes with this aspect of the cellular activity of the fibroblasts; i.e., with the formation of collagen, and in this way it facilitates the elimination of the graft. The fact that in the homograft bed

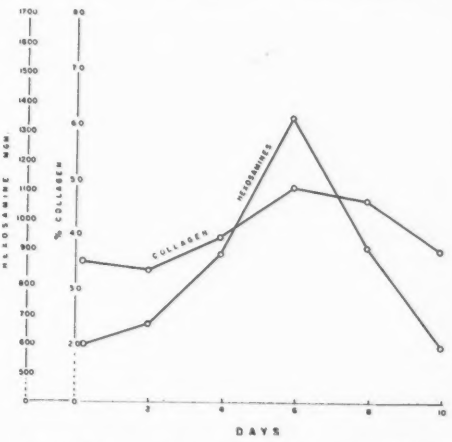

FIG. 11. Pattern of wound healing in homotransplants.

there is a dissociation of the inverse relationship between hexosamine concentration and collagen formation is of interest in the general theory of connective tissue, since so far the relationship has been observed in every instance, with the possible exception of those areas of connective tissue where variations in the amount of acid mucopolysaccharides seem to be a response to hormonal stimulation. The precipitous fall in the concentration of hexosamine that was observed in the homograft bed was not followed by a marked increase in collagen formation, and this might be interpreted as indicating that the activity of the fibroblast may be disturbed at any moment during the process of wound healing, and that the fall of hexosamine is only synchronous with the normal raise in collagen but that there is no causal relationship.

TABLE II.—COLLAGEN CONTENT OF AUTOTRANSPLANTS AND HOMOTRANSPLANTS (PER CENT OF DRY TISSUE)

Day	*Autograft*	*Homograft*
2	29.9	33.4
4	31.7	39.7
6	41.2	48.2
8	59.5	46.1
10	73.4	37.00

In 3 determinations of collagen in normal rat skin it was found that the average content was 35.8 per cent of dry tissue.
Each figure is the average of 4 determinations.

SUMMARY

The mechanism of wound healing has been studied in the graft bed of skin autotransplants and skin homotransplants by means of histologic and biochemical methods. It has been found that there is a delay in the fibroblastic reaction and that the area of proliferation of connective tissue is much smaller in the bed of the homograft. At the same time, there is a normal but lower curve of hexosamine concentration and a lack of proliferation of collagen, as shown by determinations of hydroxyproline, in the graft bed of the homotransplants. The meaning of these findings in relation to problems associated with transplantation as well as with connective tissues in general is discussed and it is pointed out that the disturbance in the fibroblastic activity may be caused by the same mechanism of rejection of the homograft and that the dissociation in the inverse relationship between hexosamine concentration and collagen formation appears to negate the role that has been suggested for the acid mucopolysaccharides in the organization of connective tissue fibers.

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THE SURGICAL TREATMENT OF AORTIC INSUFFICIENCY BY OPEN PLASTIC REVISION OF THE TRICUSPID AORTIC VALVE TO A BICUSPID VALVE

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THE METHOD of aortic valvuloplasty to be described consists of total excision of the noncoronary aortic cusp with a corresponding triangular segment of the base of the aorta. By suture repair, the normal tricuspid aortic valve is converted to a bicuspid valve and the aortic circumference is accordingly reduced by one-third. In effect, a severe degree of aortic insufficiency is produced by total excision of the noncoronary aortic cusp, and this is surgically corrected by the technique of aortic wall and valve revision. The same technique has been applied to the pulmonic valve but the details are omitted in this report. Alai reported that a defect of more than one-third of the posterior cusp is not tolerated by dogs. Operative procedures were performed under direct vision with cardiac bypass employing an extracorporeal pump-oxygenator and elective cardiac arrest.

In addition to an evaluation of mortality and survival of operated upon animals, it was an object of study to determine whether or not the reconstructed, bicuspid aortic valve produced significant degrees of dynamic aortic stenosis or aortic insufficiency. These aspects were assessed in terms of preoperative and postoperative arterial pulse curves, blood pressure determinations, and postoperative retrograde aortography as reported by Wilder.

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Previous investigations including those by DeHeer, Katz, Robinson, and Wiggers (21) have shown that in addition to alterations of arterial pulse contours, significant dynamic aortic stenosis is associated with a slight prolongation of isometric contraction and definite prolongation of the ejection phase of systole, the duration of total systole being increased, whereas aortic insufficiency is accompanied by a shortening of isometric contraction and prolongation of the ejection phase, the duration of total systole being approximately the same.

MATERIALS AND METHODS

Twenty unselected, apparently healthy, mongrel dogs (6.0 to 30 kgm.) were anesthetized with intravenous sodium pentothal and intubated. Pulmonary ventilation with room air was controlled with a mechanical, intermittently positive pressure apparatus. The blood pressure was monitored by a cannula in the left femoral artery. The right carotid artery was exposed, ligated distally, and cannulated proximally with a No. 14 French catheter for perfusion.

Right thoracotomy through the fourth or fifth interspace was performed. Umbilical tapes were passed around the superior and inferior venae cavae and ascending aortic arch respectively. The animals were heparinized 1.5 milligrams per kilogram of body weight. Catheters of appropriate size were passed into the venae cavae and connected to tubing in continuity with the extracorporeal pump-oxygenator, bubbler type, as described by DeWall and associates.

TABLE I.—RESULTS IN 20 EXPERIMENTS

Exp. No.	*Animal No.*	*Living*	*Deaths*	*Delayed deaths*	*Cause of death*	*Dicrotic arterial pulse curve*		*End-Diastolic pru. left V. mm. Hg*	*Femoral pulse pres. mm. Hg*
						Carotid	*Femoral*		
1	1169			4 days	A.I.	—	—	—	45
2	1172		D		A.I.	—	—	19	45
3	1182	L				+	+	11	45
4	1198		D		A.I.	—	—	—	32
5	1181	L				+	+	19	38
6	1194		D		A.I.	—	—	15	34
7	1199	L				+	+	19	56
8	1200		D		A.I.	—	—	39	14
9	1209		D		A.I.	—	—	19	34
10	1210		D		A.I.	—	—	5	14
11	1212		D		A.I.	—	—	29	53
12	1217	L				+	+	19	41
13	1220		D		Hemothorax	+	+	16	26
14	1193	L				+	+	11	44
15	1234			60 days	?	+	+	34	20
16	1231	L				+	—	10	38
17	1226			19 days	Bronchopneumonia	+	+	15	30
18	1240		D		P. O. tracheal obstruction	+	+	3	52
19	1238	L				+	+	0	35
20	1242			7 days	Emboli	+	+	50	85

D—Died in immediate postoperative period (30 minutes to 18 hours).
A.I.—Aortic insufficiency.

TABLE II.—DURATION OF PHASES OF SYSTOLE DETERMINED FROM FEMORAL PULSE CURVES

Animal No.	*Phase of maximal ejection,** seconds		*Phase of reduced ejection,†* seconds		*Total systole,‡* seconds	
	Preop.	*Postop.*	*Preop.*	*Postop.*	*Preop.*	*Postop.*
1199	.12	.16	.2	.2	.32	.36
1200	.08	.12	.08	**		
1210	.08	.1	.08	**		
1212	.1	.16	.1	.08	.2	.24
1217	.1	.1	.12	.12	.22	.22
1193	.16	.22	.1	.1	.26	.32
1234	.1	.1	.1	.1	.2	.2
1231	.08	.12	.1	**		
1226	.08	.08	.14	.12	.22	.2
1238	.18	.1	.1	.08	.28	.18
1242	.1	.1	.12	.16	.22	.24
1220	.06	.1	.08	.12	.14	.22
1182	.08	.08	.12	.12	.2	.2

*Includes the period of minimum ejection as given by Wiggers.
†Includes the protodiastolic phase.
‡Does not include phase of isometric contraction since simultaneous intraventricular pressures were not performed nor were synchronous heart sounds detected. Duration of systole is altered chiefly by changes in phase of systolic ejection.
**Dicrotic notch absent in descending limb of pulse curve.

Perfusion rates were 35 to 40 cubic centimeters per kilogram per minute. Perfusion times ranged between 20 and 42 minutes.

The pump-oxygenator was put into operation, and elective cardiac arrest with potassium citrate (5 to 25 c.c. of 2.5 per cent solution in heparinized blood) as described by Melrose was performed. The posterolateral aspect of the base of the aorta corresponding to the site of the noncoronary aortic cusp was incised in the long axis for approximately 2.5 to 3.0 centimeters (Fig. 1). The incision was carried to the most dependent line of attachment of the cusp. The noncoronary aortic cusp was next completely excised at its line of attachment. A somewhat triangular segment of aorta opposite the noncoronary aortic cusp was excised. The aortic valve and wall were then reconstructed by interrupted sutures approximating the annular lines of attachment of the excised noncoronary cusp, forming thereby a new commissure and a bicuspid aortic valve. The need for accurate apposi-

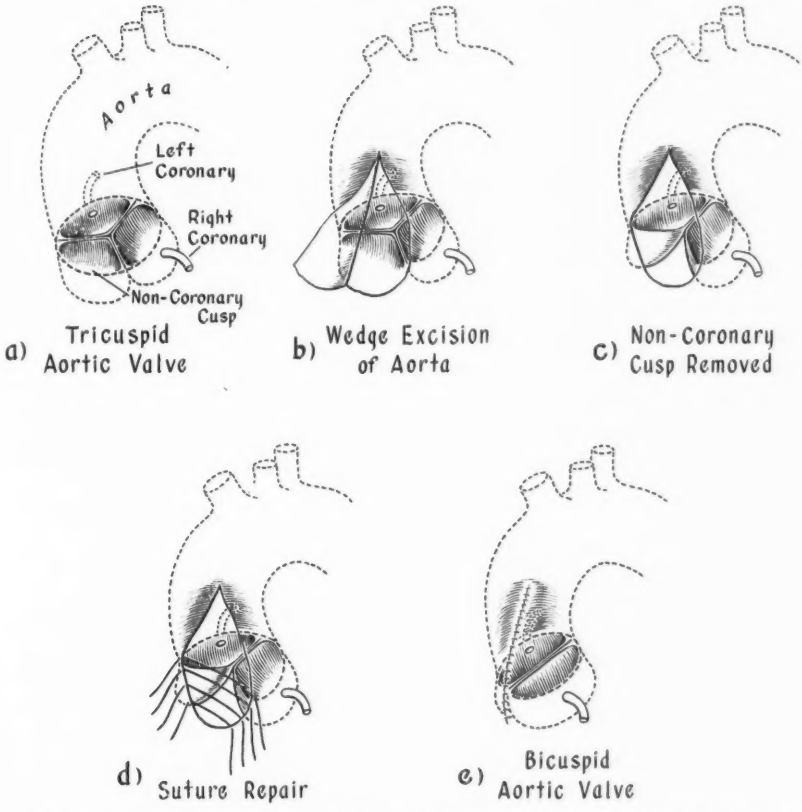

FIG. 1. Conversion of tricuspid aortic valve to bicuspid valve. Schematic drawing showing sequences in operative technique of aortic valve revision.

tion of the posterior margins of the two remaining coronary cusps became apparent following some actual experience with the method.

Arterial pulse curves and pressure determinations were made before and after valve revision with a Statham strain gauge P23A and Sanborn polyviso recorder with recording speed of 25 millimeters per second. Coronary arteriography was done via the carotid artery with sodium acetrizoate (urokon 70 per cent) 32 centimeter tube distance, 1/60 second exposure, 360 milliamperes, 50 to 65 kilovolts as previously described by us (8).

RESULTS

The results in 20 consecutive experiments are tabulated (Table I). The striking correlation between surviving animals and the presence of a dicrotic notch and dicrotic wave in the postoperative arterial pulse curve led to a more exacting coaptation of the two remaining coronary cusps (Fig. 3). The absence of the dicrotic notch and wave are indicative of dynamic aortic insufficiency. A more accurate reconstruction of the newly formed posterior commissure was made commencing with experiment 12 and dicrotic pulse curves were obtained in all subsequent studies inclusively. Wiggers (22)

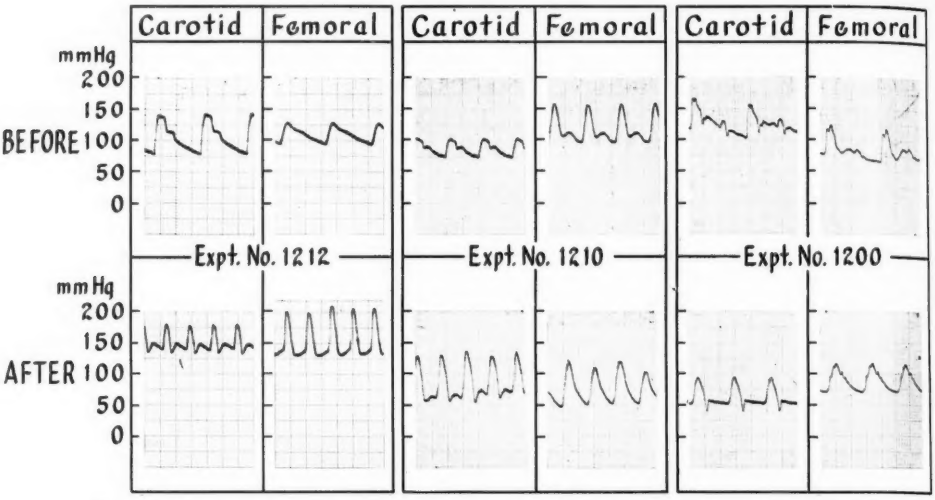

FIG. 2. Pulse curves before and after conversion of tricuspid aortic valve to bicuspid valve. Postoperative arterial pulse curves showing absence of the dicrotic notches and waves in the femoral artery. Note the abrupt upstroke in animals 1212 and 1210. The contour of the carotid artery has been changed. A bisferious character, aortic stenosis, and aortic insufficiency, is present in the femoral curve of 1200. Irregularities in the preoperative curve of 1200 are believed due to artefacts. All animals died in the immediate postoperative period as a result of dynamic aortic insufficiency.

emphasized that the details of arterial curves in experimental aortic insufficiency depend to a considerable degree on the condition of the heart and the peripheral vessels at the time the studies are produced, e.g., venous pressure, myocardial tone, vasodilatation. Cardiac bypass with total body perfusion and elective cardiac arrest are accompanied by changes, transient or prolonged, in the heart and peripheral circulation. These factors should be taken into account in the interpretation of the results. Preoperative and postoperative measurements of the duration of phases of systole are given (Table II). Measurements of the maximum ejection phase were taken from the beginning of the upstroke of the ascending limb of systole to the peak of the curve and therefore the phase of isometric contraction (.05 sec.) is excluded. The reduced ejection phase was measured from the peak of the summit to the dicrotic notch and therefore includes the protodiastolic phase (0.2 sec.). Although changes were not marked, of 13 studies made, 5 showed minor prolongations of systole and 2 showed shortening. In 3 studies there was no change while in 3 others because of the absence of a dicrotic notch total systole was not determined. Induced anacrotism was absent in all surviving animals. Bramwell has shown that acceleration of the pulse may abolish anacrotism but this does not seem to have been a factor in these experiments. The duration of the diastolic phases are charted (Table III). Marked changes are

TABLE III.—DURATION OF DIASTOLE DETERMINED FROM FEMORAL PULSES CORRELATED WITH PULSE CHANGE

	Total diastole, seconds		*Pulse rate per min.*	
Animal No.	*Preop.*	*Postop.*	*Preop.*	*Postop.*
1199	.32	.4	88	79
1200	.52	*	83	136
1210	.28	*	125	180
1212	.44	*	100	180
1217	.28	.2	150	123
1193	.16	.24	220	180
1234	.52	.24	83	125
1231	.2	*	150	136
1226	.2	.24	136	136
1238	.16	.48	187	88
1242	.28	.92	115	60

*Absence of dicrotic notch.

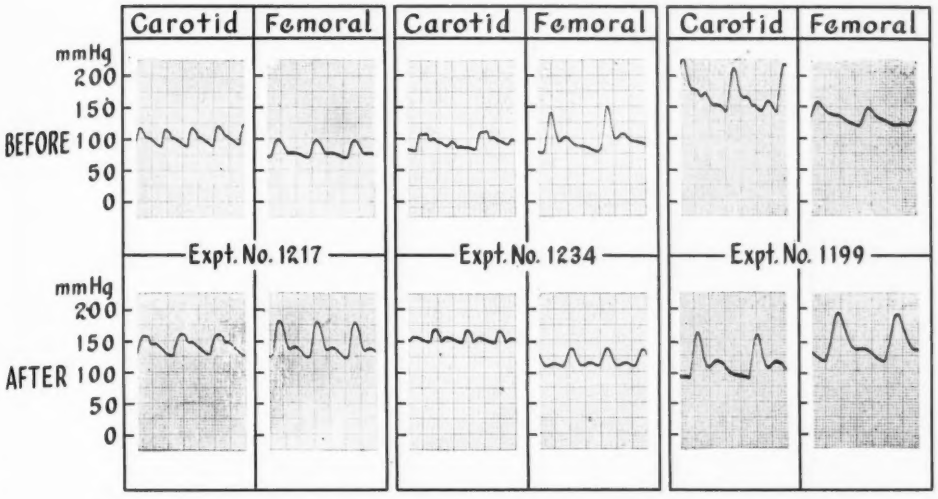

FIG. 3. Pulse curves before and after conversion of tricuspid aortic valve to bicuspid valve. Carotid and femoral artery pulse curves in 3 experiments showing presence of dicrotic notches and dicrotic waves. Animals 1199 and 1217 are alive 5 and 4 months respectively. Animal 1234 died 60 days postoperatively (cf. Table I and text).

readily correlated with alterations in the preoperative and postoperative pulse rate. The influence of the operative procedure per se is, therefore, difficult to interpret. Complications listed in Table I as hemothorax (experiment 13), bronchopneumonia (experiment 17), tracheal obstruction (experiment 18), and systemic emboli from the suture line (experiment 20) are considered preventable and do not seriously mar the potential of the procedure. Chronic survivors range between 4 to 6 months postoperatively. Experiment 15 warrants additional comment. This animal was well for 60 days and died suddenly. Autopsy disclosed concentric hypertrophy of the left ventricle. The aortic ring admitted the tip of the small finger and measured 2 centimeters in circumference. The edges of the coronary cusps were thickened and irregular. The mechanism of death was not established.

Transventricular end-diastolic pressures in the left ventricle and femoral artery pulse pressures were determined but did not provide consistent correlation between survival and mortality, nor with the arterial pulse curves (Table I). Because of the surgical approach, right thoracotomy, heart displacement was usually necessary for left ventricular puncture and seemingly minor displacements of the heart were found to modify end-diastolic pressures significantly. The significance of the end-diastolic pressure readings may be clarified in subsequent studies by combined closed chest cardiac catheterization and analysis of indicator dilution curves. Significant transvalvular systolic pressure gradients were not found and would indicate the absence of any significant aortic stenosis. Supravalvular pressures were in fact found slightly higher than ventricular pressures in some instances and this again may be related to heart displacements.

Retrograde aortography (Figs. 4 and 5) showed the character of the newly formed bicuspid aortic valve, filling of the coronary arteries, narrowing of the base of the aorta, and no apparent reflux of dye into the left ventricle when the reconstructed valve was competent.

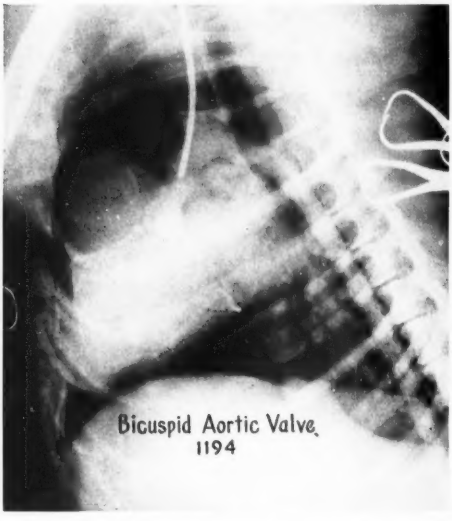

FIG. 4. Postoperative coronary arteriogram showing: bicuspid character of aortic valve, surgical narrowing of aorta, coronary artery filling, generalized opacification of left heart chambers suggesting reflux of dye. Arterial pulse curves showed absence of dicrotic notch and dicrotic wave indicating dynamic aortic insufficiency.

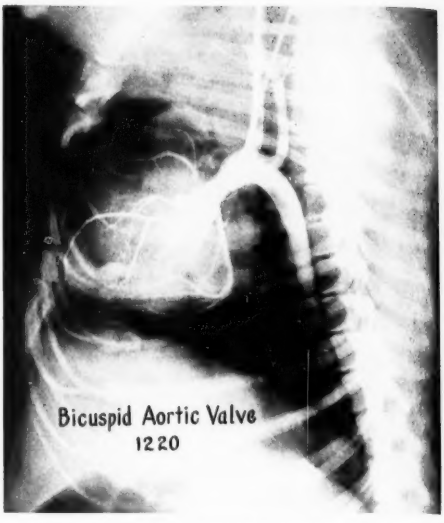

FIG. 5. Postoperative coronary arteriogram showing: the bicuspid character of the aortic valve, surgical narrowing of the aorta, coronary artery filling, the absence of dye in the left ventricle. Arterial pulse curves demonstrated the presence of dicrotic notches and dicrotic waves.

It is of interest that the high incidences of operative, gross, coronary air embolism (50 per cent) and ventricular fibrillation (95 per cent) were not seemingly deterrent to successful results. Defibrillation was accomplished electrically (120 v., 1.5 to 3 amp., 0.1 sec.).

DISCUSSION

Selected forms of aortic insufficiency are characterized by a loss of valve substance and a dilatation of the aortic valve ring. The remaining integrity of these incompetent valves at autopsy examination is variable but suggests that the proposed operative procedure or a modification may be feasible. Gorlin points out that whenever aortic-valve closure leaves a defect of 0.3 square centimeter or larger, significant regurgitation occurs with leaks of blood equal to and probably 3 times the useful or systemic cardiac output. Campbell and Hufnagel have attacked the problem by placing a prosthetic valve in the descending portion of the aorta. Bailey (3), Wible, Roe, and Malette have reported subcoronary or supracoronary prostheses. Circumferential pursing sutures below the coronary arteries have been tried by Bailey (3) and Taylor.

Other methods of treatment tried include transplantation of homologous aortic valve grafts as reported by Lam and Bailey (2) (done by us with similarly discouraging results), use of pericardial pedicles and vein grafts, injection of sclerosing solutions around the valve, and organic prostheses described by Litwak. Limitations of plastic prostheses are the distal locations in which they are placed thereby controlling only part of the regurgitation, technical difficulties encountered in placing a supracoronary or subcoronary prostheses, introduction of a foreign body subject to thrombosis in the blood stream, aneurysm formation with rupture and the traumatic cellular effect of an artificial valve in long-continued

use. The circumclusion technique was abandoned by Bailey after 43 clinical cases.

The method of treatment herein introduced is directed to an alteration of the pathologic anatomy, namely, to reduce permanently the circumference of the dilated aortic valve ring by one-third and in so doing permit the coaptation and improved function of two remaining coronary cusps. Accordingly, the normal relationship between the reconstructed aortic valve and coronary arteries is retained, no foreign body is introduced into the vascular system and no free homologous nor autogenous graft is needed.

It is readily accepted that the present experimental studies were performed on subjects in which the aortic valve at the outset was normal. Nevertheless, the excess of valve substance in the reconstructed bicuspid valves is readily apparent, suggesting that the method may be feasible and practical in diseased valves with varying degrees of loss of valve substance. Hydraulic and cinephotographic studies by the McMillan technique may clarify the value of the proposed operative procedure. Isolated disease of the noncoronary cusp, as following trauma or congenital perforation, would seemingly be suited for this type of repair.

SUMMARY

1. A method of aortic valve-plasty is described consisting of total excision of the noncoronary aortic cusp and plastic revision with conversion of the tricuspid aortic valve to a bicuspid valve.

2. Twenty consecutive animal studies are presented giving animal survival and a functional evaluation of the bicuspid aortic valve in terms of preoperative and postoperative arterial pulse patterns, transventricular and systemic pressure determinations, and retrograde aortography.

3. Eleven of 20 animals survived the immediate postoperative period. Seven animals are long term survivors (4 to 6 months). Additional long term survivors not included in this analysis have been obtained.

4. Seven of 9 animals dying in the immediate postoperative period had severe dynamic aortic insufficiency as evidenced by the absence of dicrotic arterial pulse curves in the postoperative period. (The intrinsic mortality of cardiopulmonary bypass with the use of an extracorporeal pump oxygenator in our laboratory is less than 10 per cent.)

5. A more deliberate coaptation of the newly formed commissure in the last 9 studies (experiments 12 to 20) was attended with consistent postoperative dicrotic pulse curves and improved animal survival (7 survivors of the immediate postoperative period and 2 preventable deaths).

6. No significant degree of aortic stenosis nor aortic insufficiency was produced in surviving animals.

7. Additional studies in long term survivors are in progress.

8. Possible clinical application of the principle and method for the treatment of regurgitant lesions of the aortic and pulmonic valves is suggested and supported by a pathologic study in progress.

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THE PAPILLA OF VATER AND DISTAL PORTIONS OF THE COMMON BILE DUCT AND DUCT OF WIRSUNG

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THE RECENT INTRODUCTION of operative pancreatography has furnished information about pancreatic pathology analogous to that gained in the biliary tract through cholangiography. In most of the clinical material, an ascending pancreaticogram was secured by intubating the duct of Wirsung through the papilla of Vater. Popularization of caudal pancreatectomy and pancreaticojejunostomy necessitated a descending pancreaticogram with radiopaque media instilled into the midportion of the duct of Wirsung. This investigation was undertaken in order to study radiologically the normal anatomy of the major biliary and pancreatic ducts in their distal portions, with particular emphasis on relationship to the papilla of Vater. Previous roentgen studies of these ducts have been largely concerned with the question of biliary-pancreatic reflux and the anatomy of the pancreatic radicles. The only report similar to ours is that of Cordier who in 1952 made roentgenograms of the biliopancreatic duct system of 39 cadavers after injecting opaque media into either the common or major pancreatic ducts.

METHOD

Eighty human cadavers were examined within 48 hours after death. Radiograms were taken in 52 cases without gross evidence of biliary or pancreatic disease and in 5 cases of chronic pancreatitis. The antrum, duodenum, pancreas, and inferior portion of the liver with attached gallbladder and hepatoduodenal structures were excised en bloc and affixed to a wooden frame to preserve their in vivo relations. After opening the anterior aspect of the duodenum, the papilla of Vater was measured and its ostium localized with a metal pointer. A cannula was inserted into the supraduodenal portion of the common duct at the level of the cystic duct. The body of the pancreas was transected and the duct of Wirsung was regularly located in a central position, somewhat closer to the anterior than the posterior aspect of the pancreas. A segment of polyethylene tubing, 1.57 millimeters in diameter, could be easily introduced into it. Iodized oil was instilled into both ducts simultaneously at a pressure just sufficient to produce free flow from the papilla. Aqueous opaque solutions as iodopyracet were discarded because of their tendency to diffuse into the pancreatic tissues. All films were taken at a tube distance of 6 feet to avoid distortion or magnification. From these, tracings were made of the distal portions of the common and major pancreatic ducts down to their exit into the duodenum, and the length of the papilla of Vater was inscribed on each drawing.

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PAPILLA OF VATER

There is some confusion as to what constitutes the papilla of Vater. In formal anatomic usage, the term "papilla" implies a conical eminence and refers only to that terminal free portion of the common duct which projects above the duodenal mucosa. Such a teat-like structure was present in only 4 per cent of our specimens and formed an appendage to what we have considered the papilla. Sterling describes the papilla as the solid mass of fibrous and muscular tissue

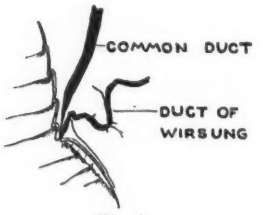

FIG. 1.

FIG. 2.

FIG. 1. Relations of distal portions of common duct and duct of Wirsung to the papilla of Vater. ×0.35.

FIG. 2. Common duct opening into the papilla of Vater and the duct of Wirsung into the lesser papilla. The lines drawn at the side of the tracing indicate the length of the papilla of Vater. ×0.35.

TABLE I.—DIMENSIONS OF PAPILLA

	Length of papilla		*Width of papilla*	
	Per cent of 50 cases	*Per cent of 100 cases (Poppel)*	*Per cent of 50 cases*	*Per cent of 100 cases (Poppel)*
1.0– 2.9 mm.	0	3	2	3
3.0– 4.9 mm.	10	1	44	14
5.0– 6.9 mm.	4	2	32	46
7.0– 8.9 mm.	5	5	14	34
9.0–10.9 mm.	14	21	6	3
11.0–12.9 mm.	22	3	2	0
13.0–14.9 mm.	22	7		
15.0–16.9 mm.	12	39		
17.0–18.9 mm.	8	4		
19.0–20.9 mm.	2	7		
21 mm. or larger	1	8		

which carries within it the distal portions of the ducts. Although all of his patients possessed what he called papillae, a demonstrable prominence above the mucous membrane of the duodenum was present in only 76 per cent. In common with Poppel, we have found the papilla to be a well circumscribed mucosal elevation in all of our fresh specimens. This structure is not conical but a hemisected cylinder shaped like a Quonset hut with an average length of 11.7 millimeters and width of 5.2 millimeters. It usually forms the anteriolateral wall of the distal portion of the common duct and of the ampulla. The height of the papilla could not be accurately measured but appeared to be slightly less than its width (Table I).

The largest normal papilla in our series measured 21 millimeters long with a width of 10 millimeters; 1 in Poppel's series was 30 by 12 millimeters. Size of the papilla alone, is not a criterion of disease. In agreement with Cordier, we could not identify the normal papilla by palpation through the intact duodenum, and only rarely can it be felt by the exploring finger through an open duodenotomy. Suspected nodules usually prove to be either prominent pancreatic lobules or ectopic pancreatic rests. In our clinical experience, a papilla palpable through the unopened duodenum without being extruded over a probe was invariably the site of papillitis, hypertrophy, or neoplasm.

The ostium of the papilla is classically located in the midportion of the descending duodenum. In common with other observers we have found it more often below this

FIG. 3. Common duct and duct of Wirsung opening side by side at the papilla. ×0.5.

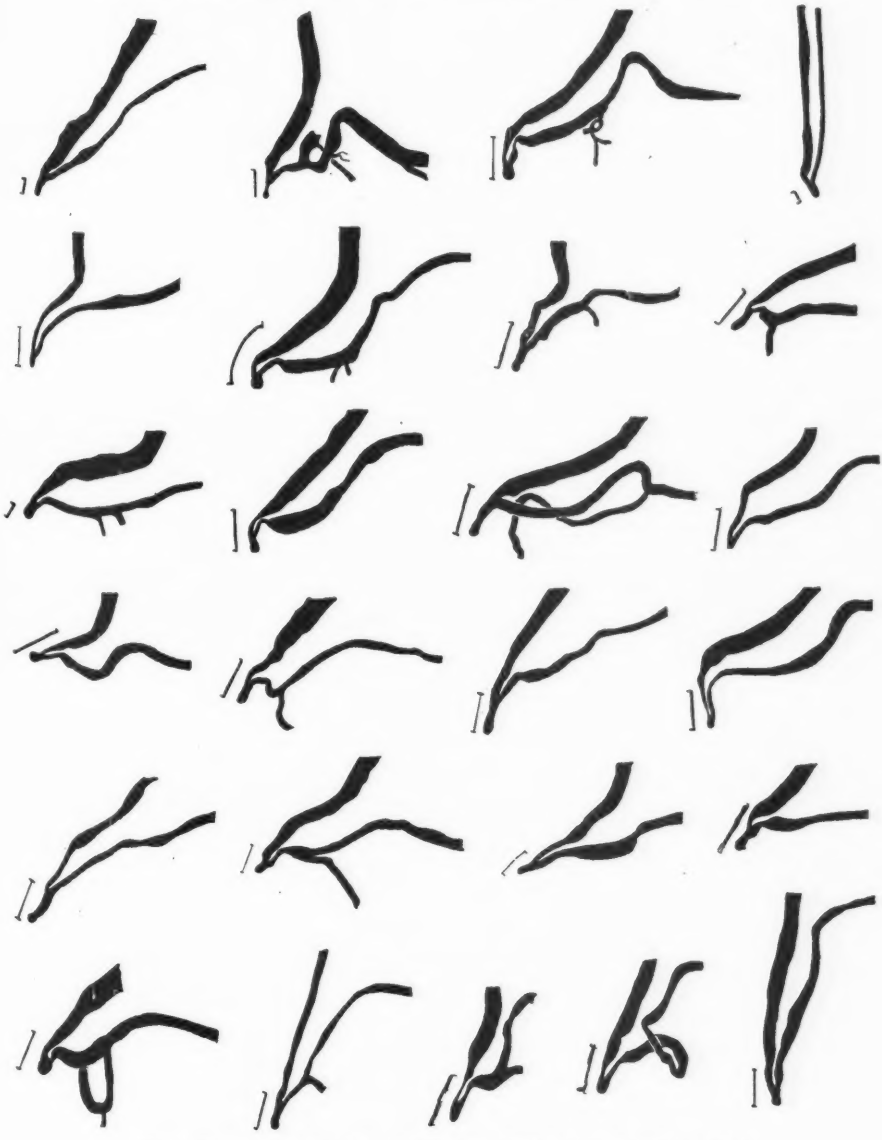

FIG. 4. Common duct and duct of Wirsung opening into an ampulla. ×0.5.

point. Its average distance from the usual site of a supraduodenal exploratory choledochotomy measured 83.3 millimeters with a span between 55 and 122 millimeters (Table II). The papilla is consistently in the posteromedial quadrant of the opened duodenum and dorsal to a prominence produced by the head of the pancreas as it

TABLE II.—LOCATION OF PAPILLA

DISTANCE BETWEEN OSTIUM OF PAPILLA AND SUPRADUODENAL PART OF COMMON DUCT	*Per cent of cases*
50– 59 mm.	4
60– 69 mm.	12
70– 79 mm.	32
80– 89 mm.	26
90– 99 mm.	14
100–109 mm.	10
110–119 mm.	0
120–129 mm.	2

LOCATION OF THE PAPILLA IN DUODENUM	*Lurje (194 cases) Per cent*	*Kantor (112 cases) Per cent*
Upper half, descending duodenum.	4.2	0
Midportion, descending duodenum.	38.1	36.0
Lower half, descending duodenum.	49.5	60.4
Junction between descending and third part of duodenum.		3.6
Third part of duodenum.	8.2	

invaginates the medial wall of the duodenal concavity. It runs parallel to the long direction of the bowel but occasionally has an oblique course with its cranial end medial to its caudal extremity. In 1 of our cases, the papilla ran a semilunar course. One or two valvulae conniventes cross the papilla transversely and frequently but not invariably a vertical frenum of mucosa passes downward from the inferior margin of its ostium. In all cases, the opening into the papilla faces downward rather than anteriorly (Fig. 1).

In 1 case, the duct of Wirsung emptied through the lesser papilla (Fig. 2) and in all of the remaining, both it and the common duct opened on the papilla of Vater. In 5 of the latter, separate openings could be visualized at the papilla (Fig. 3). An ampulla, or common anatomic channel, was therefore present in 88 per cent of our normal material (Fig. 4). A lower frequency has been reported by those who dissected fixed material (Table III). In 80 per cent of our specimens, the ampulla was 3 or more millimeters in depth when measured from the surface of the papilla to the septum between the two ducts (Table V).

In 7 cases, the junction of the common duct and duct of Wirsung was appreciably proximal to the papilla (Fig. 5). Therefore,

TABLE III.—RELATIONS BETWEEN COMMON DUCT DUCT OF WIRSUNG, AND PAPILLA OF VATER

No. of cases	*Type I, per cent*	*Type II, per cent*	*Type III, per cent*	
Dissection				
50	60			Baggenstoss
90	67			Baldwin
50	74			Chodkowski
25	32			Couvelaire
100	49			Dardenille
100	48	51	1	Dardinski
50	22	48	20	Holzapfel
30	63			Hughes
151	5			Job
114			6	Keyl
21	38	57	5	Letulle
200	65	31	4	Mann
449	61	34	5	Mehnen
100	60	33	7	Naatanen
57	90	8	2	Nagai
75	76	19	5	Nuboer
100	77	11	12	Opie
100	26			Pedro-Bellou
36	58			Poppel
250	74	24	2	Rienhoff
43	74	26	0	Ruge
47	53	47	0	Schirmer
64			6	Schwarz
45	58			Smith
50	36	64	0	Sterling
58	98		2	von Bugner
48	50	31	19	Werthemann
50	74			Wohrmann
Perfusion studies				
100	74			Cameron
150	73			Howard
X-rays with papilla obstructed				
100	86	6	8	Hjorth
200	85.5	5.5	9	Millbourn
X-rays without papillary obstruction				
23	35	65		Cordier
50	88	10	2	Newman

Type I, ampulla.
Type II, ducts open separately at papilla.
Type III, duct of Wirsung opens into lesser papilla.

the major pancreatic duct could be intubated under direct vision at the papilla in 10 per cent and after papillotomy in an additional 74 per cent of the cases. When the two ducts open side by side, the pancreatic ostium is anteromedial to that of the common duct. When the duct of Wirsung empties within the papilla, the pancreatic opening is usually on the medial wall. In 6 per cent of the specimens, the pancreatic duct joined the anterior aspect of the common duct (Fig. 6) and in 4 per cent the duct of Wirsung circumscribed the distal part of the common duct posteriorly to open on its lateral aspect

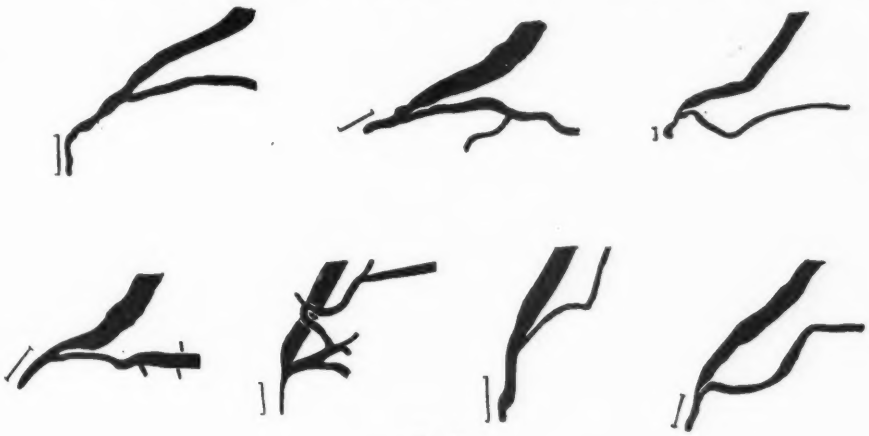

FIG. 5.

FIG. 6.

FIG. 5. The duct of Wirsung joining the common duct proximal to the papilla. ×0.5.
FIG. 6. The duct of Wirsung opens into the anterior aspect of the common duct. ×0.5.

(Fig. 7). In Cordier's 23 cases, an anterior junction was present in 6 and a posterior in 1 case.

DISTAL PART OF THE COMMON DUCT

Cholangiography in the cadaver reveals a funneling of the distal portion of the common duct prior to its entrance in the duodenal window similar to that observed in the living. The duct lumen is usually narrowest at some point proximal to the papilla and may widen if an ampulla is present. In 34 per cent of our specimens, the narrowest portion of the common duct lay within the papilla. This tapering is produced by the superior constrictor fibers of the choledochal component of the sphincter of Oddi described by Boyden. In two-thirds of our normal specimens, a complete sphincterotomy would entail an extension of the incision in the papilla beyond the wall of the duodenum. When sphincterotomy is performed over a probe passed down the common duct, this narrowed muscular portion may be extruded into the duodenum to give the fallacious impression that all of the choledochal muscle fibers lie within the papilla.

An intact papilla prevents regurgitation of duodenal contents into the biliary tract by a valve-like mechanism produced by its intramural course. In 10 cadavers we elevated the intraduodenal pressure to 1,500 millimeters of water without evidence of regurgitation because the rising intraduodenal pressure compressed the lumen of the papilla. Caroli found only 2 instances of spontaneous regurgitation through an undiseased papilla; in both cases the common duct emptied anomalously into the duo-

FIG. 7. The duct of Wirsung winding about the common duct. ×0.47.

denum without an oblique intramural course. In one, the duct opened into the first part of the duodenum, and in the other it ran a straight course into the third part of the duodenum.

For some clinical disorders, sphincterotomy has been preferred to a biliary-intestinal anastomosis on the theory that the former operation is not followed by regurgitation or cholangitis. In the cadaver, we could regularly induce regurgitation into the common duct by increasing intraduodenal pressure and excising the papilla down to the point where the common duct enters it, even though we remained within the confines of the intrinsic musculature of the duodenum. In 2 of our patients with chronic pancreatitis, in whom a similar procedure was performed, air could be demonstrated in the biliary tract 6 months after operation.

THE DUCT OF WIRSUNG

The duct of Wirsung maintains a fairly constant diameter through the body, neck, and head of the pancreas until it approaches the papilla where it may narrow slightly but the funneling seen in the common duct occurs infrequently. Leger's microscopic studies deny the importance of an intrinsic pancreatic sphincter. In some of our normal specimens, there was a slight dilatation of the duct just proximal to this narrowed terminal segment. The average diameter of the widest portion of the normal duct of Wirsung measured 3.5 millimeters (Table IV).

TABLE IV.—MAXIMAL WIDTH OF THE DUCT OF WIRSUNG

Width	*Per cent of cases*
1.0–1.9 mm.	8
2.0–2.9 mm.	28
3.0–3.9 mm.	36
4.0–4.9 mm.	16
5.0 mm.	12

In 5 additional cases, although the pancreas appeared grossly normal, there was an unusual dilatation of the major pancreatic duct which reached 10 millimeters in 1 case. Microscopy in 3 of these cases revealed slight chronic pancreatitis. In all 5 there was some radiologic evidence of duct narrowing distal to the point of dilatation (Fig. 8). In all the normal specimens and in 4 out of 5 of the cases of pancreatitis, the diameter of the common duct exceeded that of the duct of Wirsung. In 4 other specimens, there was some dilatation of the common duct while the pancreatic duct remained normal (Fig. 9). This observation may be explained by hyperactivity restricted to the choledochal component of the sphincter of Oddi.

The duct of Santorini was rarely visualized at our low perfusion pressure. In several specimens, the papilla was obturated and the iodized oil injected with considerable force. This procedure often brought into view the duct of Santorini and an unnamed descending vertical branch to the head of the pancreas. The major ducts are only slightly distensible to acute rises in pressure, which is

TABLE V.—DEPTH OF THE AMPULLA OF VATER

	No. of specimens	*No ampulla*	*Depth in millimeters*									
			Below 3	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11 or more*
Baggenstoss	55	22	11	3	13	5	0	1	0	0	0	0
Cameron	86	26	12	0	0	8	12	13	6	2	3	4
Dardinski	100	53	17	12	10	4	0	0	0	0	4	0
Mann	200	70	90	28	5	3	0	1	2	0	1	0
Poppel	36	15	8	4	5	4	0	0	0	0	0	0
Rienhoff	250	77	92	34	17	11	8	3	3	1	0	4
Smith	45	19	5	7	4	4	0	2	1	2	0	1
Newman	50	6	4	7	3	4	2	3	4	3	2	12

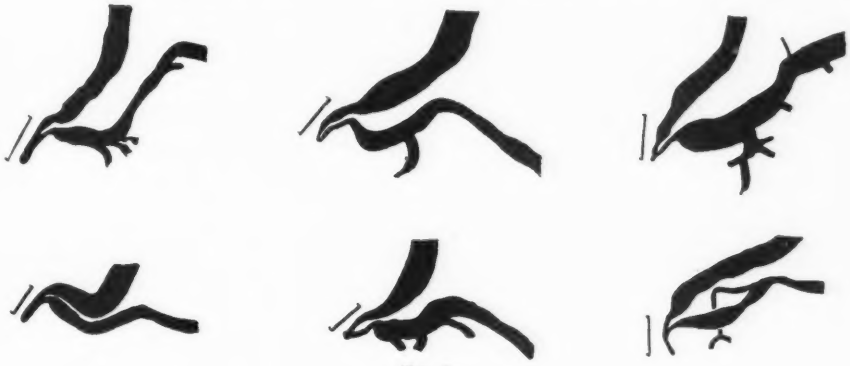

FIG. 8.

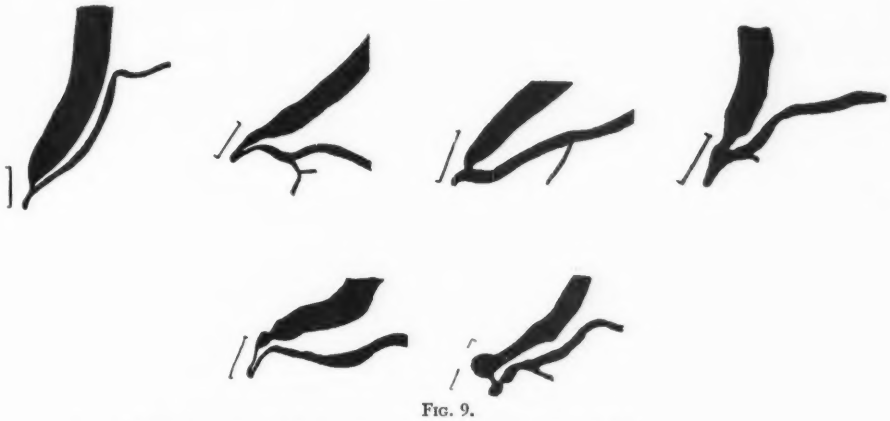

FIG. 9.

FIG. 8. Dilated pancreatic ducts as seen in chronic pancreatitis. ×0.5.
FIG. 9. Dilatation of the common bile duct without dilatation of the duct of Wirsung. ×0.5.

largely reflected by the visualization of subordinate radicles.

Du Val has suggested manometric studies through a catheter entering through the midportion of the duct of Wirsung. Although cadaver investigations offer criteria inapplicable to the living, they do furnish some idea of the hydrostatic resistance of the inert, distal reaches of the common duct and duct of Wirsung. Because of the narrowness of the polyethylene tubing, its resistance must be subtracted from the measured pressure head for a fixed rate of flow. In 5 cadavers, perfused at a rate of 10 cubic centimeters of water per minute, the duct of Wirsung offered a resistance similar to that gained from the common duct, i.e., 10 to 30 millimeters of water.

Regurgitation of intestinal contents into the pancreatic ducts is also prevented by the valvular mechanism of the papilla and additionally by the angular course of the terminal part of the duct of Wirsung. We could not induce regurgitation into the pancreatic duct in the cadaver by papillotomy as we succeeded with the common duct. Hicken reported that radiopaque media injected into the common duct may enter the pancreatic duct, even when the two open at different points in the duodenum, and

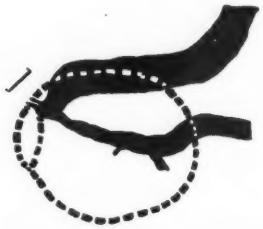

FIG. 10. Relation of diverticulum of the duodenum (dotted figure) to the papilla of Vater and ducts. ×0.5.

postulated synchronous relaxation of the sphincters governing these ducts. We have never observed reflux of barium or air into normal pancreatic ducts.

In 1 specimen, there was a diverticulum arising in its usual location from the medial aspect of the second part of the duodenum (Fig. 10). The terminal part of the common duct and the papilla formed the postero-superior border of the neck of the sac. The diverticulum was embedded in the anterior surface of the pancreas. When it was opened and the pancreatic duct distended under considerable pressure, a ridge appeared in the floor of the diverticulum. Apparently the duct of Wirsung bore a close relation to the posterior surface of the diverticulum. Diverticulectomy in such a case would be fraught with danger.

SUMMARY

1. The anatomy of the distal portions of the common bile duct and duct of Wirsung in relation to the papilla of Vater was investigated radiologically.

2. Clinical applications to the physiology and surgery of the sphincter of Oddi are described.

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FIVE YEAR SURVIVAL AFTER ANTERIOR RESECTION FOR CARCINOMA OF THE RECTUM AND RECTOSIGMOID

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THE PURPOSE of this study is to add a report of 2 more years' experience to a similar analysis reported in 1956[1]. When one attempts to determine trends in the attack on certain problems and their significance in terms of results, numbers of cases assume a very definite value. Five year survival after various operative procedures is by no means a perfect criterion on which to base definite conclusions concerning the best method of dealing with the individual case; however, it does have significance if, in given anatomic regions, an operation can be performed which is justified by survival rates comparable to those obtained by other procedures and which, in addition, preserves an important function to make postoperative life more tolerable to the patient. Cases in which surgical extirpation of carcinoma of the rectum and rectosigmoid was performed at the Mayo Clinic in the years 1945 through 1949 have been reported and similar cases for the years 1950 and 1951 are added in this report.

Follow-up studies on combined abdominoperineal resection and two stage posterior resection for the years 1950 and 1951 are not available at this time. Therefore, the results of anterior resection performed here from 1945 through 1951 will be compared with the results of combined abdominoperineal resection and two stage posterior resection performed from 1945 through 1949. It is our belief that this difference of 2 years in the two series of cases will have a minimal effect on the analysis.

From the Section of Surgery, Mayo Clinic, and Mayo Foundation, Rochester, Minnesota.

MATERIALS AND METHODS

Records of all patients who had undergone anterior resection at the Mayo Clinic in 1950 and 1951 were reviewed. Those cases in which the surgeon considered the operation to be palliative because of malignant tissue that was not excised or because of palpable hepatic metastasis were not included. This left 171 cases suitable for study.

This series of 171 cases of anterior resection performed in the years 1950 and 1951 first was compared with 336 cases of anterior resection performed from 1945 through 1949. The age and sex of the patients, the proctoscopic level of the lesions, and the grade of malignancy were essentially the same in both groups. During the 5 year period, 1945 through 1949, there were 15 hospital deaths among the 336 patients, giving a hospital mortality rate of 4.5 per cent. For the 2 year period, 1950 through 1951, there were 10 hospital deaths among the 171 patients, giving a mortality rate of 5.8 per cent. The 5 year survival rate was 3.5 percentage points better in the series of cases in 1950 and 1951 than it was in the series from 1945 through 1949, as shown in Table I. Among the female patients who were operated on in 1950 and 1951, the 5 year survival rate was better by 16 percentage points than it was among the males, whereas in the previous series of cases there was a difference of only 6.2 percentage points in favor of female patients. These two series of cases were added together to form a total of 507 cases of anterior resection.

TABLE I.—FIVE YEAR SURVIVAL RATES ACCORDING TO SEX: ANTERIOR RESECTION

	1945–1949		1950–1951	
Sex	*Total patients*	*Lived 5 years or more after operation, per cent**	*Total patients*	*Lived 5 years or more after operation, per cent**
Males	157	55.8	92	55.6
Females	164	62.0	69	71.6
Total	321	58.9	161	62.4

*Based on traced patients. Inquiry as of January 1, 1957. Hospital deaths are excluded in the calculation of survival rates.

TABLE II.—DISTRIBUTION OF LESIONS AND INCIDENCE OF METASTASIS ACCORDING TO PROCTOSCOPIC LEVEL OF LESION, ANTERIOR RESECTION, 1945–1951

	Total		With metastasis	
Distance from dentate margin, cm.	*No.*	*Per cent*	*No.*	*Per cent*
0– 5	7	1.4	5	71.4
6– 9	104	20.5	53	51.0
10–14	348	68.6	157	45.1
15–19	38	7.5	17	44.7
20 plus	10	2.0	8	80.0
Total	507	100.0	240	47.3

TABLE III.—INCIDENCE BY OPERATION AND MICROSCOPIC GRADE OF MALIGNANCY (BRODERS)

Grade	*Anterior resection, per cent of 507 patients*	*Combined abdominoperineal resection, per cent of 612 patients*	*Posterior resection, per cent of 215 patients*
1	40.6	39	44
2	51.1	49	44
3	7.7	9	7
4	0.6	3	5
Total	100.0	100	100

AGE AND SEX

Sixty-six and two-tenths per cent of the patients were in the age group of 50 to 69 years.

More men than women in the group for 1950 and 1951 underwent the sphincter-saving operation. In the combined groups of patients, there was almost an equal number of men and women. The relative increase in the number of men who underwent operation would appear to be the result of improvement in technique which makes low anterior resection possible in the narrow male pelvis.

LOCATION OF LESION

As shown in Table II, 89.1 per cent of the lesions were situated in the controversial segment of the bowel, 6 to 14 centimeters from the dentate margin.

INCIDENCE OF METASTASIS BY LOCATION OF LESION

The incidence of metastasis to lymph nodes appeared to be higher in cases in which the lesions were situated lowest in the bowel, although the number of lesions in the highest and lowest segments of the bowel was small (Table II).

INCIDENCE BY GRADE OF MALIGNANCY

All lesions were graded on the basis of degree of microscopic cellular differentiation, according to Broders' method. Ninety-one and seven-tenths per cent of the lesions were of low grade (grades 1 and 2) and 8.3 per cent were of high grade (grades 3 and 4). This is not a significant difference from the grades of malignancy in the comparable series of one stage combined abdominoperineal resection and two stage posterior resection, in which groups 88 per cent of the lesions were of low grade, as shown in Table III.

SURVIVAL

Only 6 patients among the total of 507 who had undergone anterior resection were untraced over a 5 year period, giving a traceability rate of approximately 99 per cent. The 5 year survival rate for 476 traced patients (25 hospital deaths excluded) was 60.1 per cent (Table IV). This compares to a 5 year survival rate of 51.7 per cent for those treated by one stage combined abdominoperineal resection and of 46 per cent for those treated by two stage posterior resection. After anterior resection, the 5 year survival rate is better for women than for men (Table V).

Of the patients without nodal metastasis, 73.1 per cent lived 5 years, and of those with metastasis, 46.3 per cent lived 5 years (Table VI). As shown in Table VII, the survival rate decreased as the growths approached the dentate line. This may reflect

TABLE IV.—FIVE YEAR SURVIVAL RATES ACCORDING TO OPERATION

Operation	Traced patients	Survival rate, per cent
Anterior resection	476	60.1
Combined abdominoperineal resection	580	51.7
Posterior resection	211	46.0

TABLE V.—FIVE YEAR SURVIVAL RATES ACCORDING TO SEX, ANTERIOR RESECTION, 1945–1951

	Patients		Lived 5 years or more after operation	
	Total	Traced	No.	Per cent*
Males	249	246	137	55.7
Females	233	230	149	64.8
Total	482	476	286	60.1

*Based on traced patients. Inquiry as of January 1, 1957. Hospital deaths are excluded in the calculation of survival rates.

the increased incidence of metastasis among the cases in which the lesions were lowest in the bowel.

In Table VIII, comparison is made of survival rates for different types of operation performed for lesions situated in the controversial segment of bowel, namely that portion from 6 to 14 centimeters from the dentate line. When metastasis was not present with lesions situated at levels from 10 to 14 centimeters the 5 year survival rates were 75 per cent for anterior resection, 64 per cent for one stage combined abdominoperineal resection, and 53 per cent for two stage posterior resection. When comparison was made of all cases in which nodal metastasis was present, anterior resection was associated with a higher survival rate than were the other procedures.

It was shown previously that concomitant proximal colostomy does not produce any significant decrease in operative mortality rates but it does cause the patient's stay in the hospital to be more than double that of patients who do not undergo concomitant colostomy. It is our opinion that the passage of stools is an important factor in re-establishing the normal diameter of the bowel at the site of anastomosis. This has been observed often by the proctologists.

COMMENT

These statistics are presented in order to demonstrate that adequate radical resection

TABLE VI.—FIVE YEAR SURVIVAL RATES ACCORDING TO OPERATION AND METASTASIS

	Anterior resection		Combined abdominoperineal resection		Posterior resection	
	Traced patients	Survival rate, per cent	Traced patients	Survival rate, per cent	Traced patients	Survival rate, per cent
Metastasis	231	46.3	273	34	100	26
No metastasis	245	73.1	307	67	111	64
Total	476	60.1	580	52	211	46

TABLE VII.—FIVE YEAR SURVIVAL RATES ACCORDING TO PROCTOSCOPIC LEVEL OF LESION, ANTERIOR RESECTION, 1945–1951

Distance from dentate margin, cm.	Patients		Lived 5 years or more after operation	
	Total	Traced	No.	Per cent*
0– 5	6	6	1	16.7
6– 9	96	95	52	54.7
10–14	337	333	204	61.3
15–19	34	33	24	72.7
20 plus	9	9	5	55.6
Total	482	476	286	60.1

*Based on traced patients. Inquiry as of January 1, 1957. Hospital deaths are excluded in the calculation of survival rates.

TABLE VIII.—FIVE YEAR SURVIVAL RATES ACCORDING TO OPERATION AND METASTASIS OF LESIONS 6 TO 14 CENTIMETERS FROM THE DENTATE MARGIN

Distance from dentate margin, cm.	Anterior resection		Combined abdominoperineal resection		Posterior resection	
	Traced patients	Survival rate, per cent	Traced patients	Survival rate, per cent	Traced patients	Survival rate, per cent
Without metastasis	224	73	152	57	65	66
6– 9	44	64	108	69	46	72
10–14	180	75	44	64	19	53
With metastasis	204	46	165	39	59	25
6– 9	51	47	111	41	40	25
10–14	153	45	54	35	19	26
Total (6–14)	428	60	317	53	124	47

of carcinoma of the upper rectum and rectosigmoid does not require removal of the rectal sphincter in all cases. The decision as to whether or not the sphincter should be sacrificed in individual cases must be made by the surgeon. The decision must be based on the technical feasibility of removing the lesion from above and of excising the intestine far enough below the lesion to accomplish complete extirpation of any distal spread. When this is possible, the surgeon is justified in selecting the sphincter-saving

procedure. Anterior resection usually is a difficult procedure at best and is impossible without instruments of appropriate length, namely, 12 or 14 inches long.

CONCLUSIONS

The results in 507 patients with carcinoma of the rectum and rectosigmoid treated by sphincter-saving anterior resection were compared with results obtained in similar patients treated by sphincter-sacrificing procedures. It was concluded that the sphincter-saving operation compares favorably from the curative standpoint with one stage combined abdominoperineal resection or two stage posterior resection performed for lesions in the controversial segment of the bowel; that is, those situated between 6 and 14 centimeters from the dentate margin.

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THE NATURAL HISTORY OF THE PATIENT WITH CIRRHOSIS OF THE LIVER WITH ESOPHAGEAL VARICES FOLLOWING THE FIRST MASSIVE HEMORRHAGE

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THE SURGICAL LITERATURE is replete with testimonials concerning the efficacy of portacaval anastomosis as a means of therapy for the cirrhotic patient with bleeding esophageal varices. While a few authors have questioned the exact mechanism and exact value of this procedure, it would certainly be fair to say that the majority of surgeons believe that the operation is a good one and that it functions by lowering the pressure within the portal system.

In a recent publication Hallenbeck and Shockett, quoting Child, point out that "unselected patients used to study the natural history of cirrhosis are not similar to the groups of patients with cirrhosis selected for portacaval shunting and cannot be used as a standard against which to measure the effectiveness of portacaval shunts in prolonging the life of the cirrhotic."

In the present article data are presented on the fate of all patients with cirrhosis who entered the San Francisco Hospital from June 1947 to June 1957 who survived their first massive gastrointestinal hemorrhage and who were eligible for portacaval anastomosis on the basis of Linton's criteria, but in whom the operation was not done. The essential data are presented in Tables I, II, and III.

DISCUSSION

The data from this hospital show that about 21 per cent of all patients with cirrhosis enter because of massive hemorrhage. Of this group, 338 or 74 per cent died after this first hemorrhage, leaving 118 patients for whom treatment was possible. When this group was sifted by using the criteria generally acceptable for portacaval anastomosis, 40 patients remained. Of these 40 patients, 23 are known dead, but 8 survived more than 3 years. One patient survived 13 years, finally dying in hepatic coma.

Thirteen patients are alive, 7 for more than 5 years. Four patients have been lost to follow-up.

It would appear that about one-third of all patients who have survived the first hemorrhage and who qualify for portacaval

TABLE I.—THE CAUSE OF DEATH IN 1,054 PATIENTS DYING WITH CIRRHOSIS AT SAN FRANCISCO HOSPITAL (1947–1957)

	Deaths		*Deaths verified by autopsy*	
	No.	*Per cent*	*No.*	*Per cent*
Hepatic failure	433	41	175	36
G.I. bleeding (presumed varices)	338	32	149	30
Other causes	283	27	165	34
Arteriosclerotic heart disease	48		18	
Trauma	36		36	
Tuberculosis	35		16	
Cerebral vascular accident	31		11	
Cancer (not including liver)	27		14	
Pneumonia	18		9	
Renal failure	13		8	
Hepatoma	11		11	
Infection	10		8	
Rheumatic heart disease	9		1	
Complication of peritoneal tap	7		7	
Pancreatitis	6		5	
Bleeding ulcer	6		6	
Perforated ulcer	5		2	
Poisoning	3		3	
Beriberi	3		2	
Postoperative complications	2		1	
Pulmonary embolus	2		1	
Miscellaneous	11		6	
Total	1054		489	

Autopsy rate 46 per cent.

From the Stanford University Surgical Service and the San Francisco Hospital Unit of the Department of Public Health. Aided in part by Grant 2278, U.S. Public Health Service.

TABLE II.—FATE OF 40 CIRRHOTICS WITH MASSIVE HEMORRHAGE WHO SATISFIED ESTABLISHED CRITERIA FOR PORTACAVAL ANASTOMOSIS

History No.	*Age, color, and sex*	*Total hemorrhages*	*Dates of bleeding*	*Survival*	*Cause of death*
			DEATHS		
1. N123094	67 W F	2	7/53, 9/53	2 months	G.I. hemorrhage
2. N20612	43 C F	2	5/50, 2/53	13 years	Hepatic failure
3. N43236	46 W F	8	6/46, 2/51, 8/51, 6/52, 8/52, 2/54, 2/55, 1/57	11 years	G.I. hemorrhage
4. N150567	67 W M	2	4/56, 8/56	5 months	G.I. hemorrhage
5. N144692	44 W M	2	11/55, 12/55	1 month	G.I. hemorrhage
6. N144876	47 W M	2	9/55, 11/55	6 months	Unknown
7. N85403	57 W F	2	4/54, 5/55	13 months	G.I. hemorrhage
8. N61432	71 W M	2	3/48, 11/48	8 months	G.I. hemorrhage
9. N60945	51 W F	3	9/50, 12/50, 4/51	7 months	G.I. hemorrhage
10. N67126	49 W F	3	6/53, 10/53, 1/54	7 months	G.I. hemorrhage
11. N53415	28 C F	6	3/55, 7/55, 11/55, 3/56, 8/56, 10/56	19 months	G.I. hemorrhage
12. N40861	38 W M	5	9/46, 5/47, 4/48, 8/48, 5/49	3 years	G.I. hemorrhage
13. N44386	66 W M	2	10/46, 7/49	3 years	G.I. hemorrhage
14. N33373	53 W M	2	8/49, 1/50	5 months	G.I. hemorrhage
15. N135691	39 C M	1	10/54	8 months	?Hepatic failure
16. N134231	84 W M	2	8/54, 9/54	8 months	Unknown
17. N123276	55 W M	4	8/53, 8/56, 10/56, 10/56	5 years	Cancer lung
18. N125580	45 W M	1	1/55	6 months	Appendicitis with peritonitis
19. N102793	54 C M	1	5/55	9 months	Subdural hematoma
20. N104082	38 W F	2	10/51, 8/54	3 years	G.I. hemorrhage
21. N93034	67 W M	3	10/50, 3/51, 9/51	11 months	G.I. hemorrhage
22. N99644	71 W M	6	6/51, 7/53, 2/54, 7/54, 8/5, 11/56	6 years	Carcinoma liver
23. N35244	57 W M	1	11/47	7 years	Unknown
			SURVIVALS		
1. N69322	43 W M	8	1/53, 6/53, 7/53, 2/54, 11/54, 5/55, 8/55, 6/56	4 years	
2. N82964	45 C M	4	12/49, 11/50, 6/52, 9/52	8 years	
3. N92425	42 W M	2	3/52, 8/52	5⅓ years	
4. N65392	54 W F	5	10/50, 11/50, 12/50, 2/51, 10/51	7 years	
5. N147221	26 W M	4	12/56, 7/56, 10/56, 3/57	1 year	
6. N142892	56 W F	3	7/55, 9/55, 11/55	2 years	
7. N133386	65 W M	1	7/54	3⅓ years	
8. N159773	54 W M	2	4/57, 10/57	7 months	
9. N120690	70 W M	2	5/53, 5/57	4 years	
10. N100813	40 W M	2	9/52, 11/52	5 years	
11. N81561	41 W F	1	10/49	8 years	
12. N78391	55 W M	1	7/49	8 years	
13. E115337	50 W M	5	10/46, 9/48, 2/50, 3/52, 3/54	11 years	
			LOST TO FOLLOW-UP		
1. N132497	69 W M	3	5/50, 2/53, 6/54		
2. N93109	51 W F	1	9/51		
3. N67008	68 W M	2	8/48, 2/49		
4. N46841	62 W M	4	1/47, 6/48, 9/48, 2/49		

TABLE III.—CIRRHOSIS WITH BLEEDING

	No.
Total No. of patients (June 1947 to June 1957)	2,377
No. with massive hemorrhage	507
Presumed varices	456
Gastric or duodenal ulcer	51
Deaths	338
On first bleeding	290
On second bleeding	32
On third bleeding	7
On fourth bleeding	4
On fifth bleeding	2
On sixth bleeding	1
On seventh bleeding	1
On eighth bleeding	1

It is of interest that of the patients dying of gastrointestinal hemorrhage, 86 per cent did so on the first bleeding episode.

anastomosis on the basis of present-day accepted clinical and laboratory criteria will survive 5 years and that one-third of this same group will die of gastrointestinal hemorrhage.

In a similar study, Palmer and associates reported on 48 control patients. Unfortunately, 24 patients in this group of 48 had not bled prior to the start of their series.

SUMMARY

1. Of the clinical type of patients seen at the San Francisco Hospital, 86 per cent with cirrhosis of the liver die after their first massive hemorrhage.

2. The type of patient with the least hepatic impairment who survives the first hemorrhage has a 30 per cent chance to survive 5 years on medical therapy alone.

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A STUDY OF THE EFFECTIVENESS OF "HIGH PRESSURE" CARDIOPNEUMONOPEXY IN MYOCARDIAL REVASCULARIZATION

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THIS STUDY was designed to evaluate the effectiveness of systemically arterialized lung as a means of myocardial revascularization. The various other "pexies" which have been used in the past are probably considerably less vascular than simple cardiopneumonopexy. This latter operation has been performed by others without any attempt to correct the existing arterial pressure differential between the pulmonary and myocardial circulations. This has been done despite the conceptual difficulties in understanding how blood at a pulmonary arteriolar pressure of approximately 20 millimeters of mercury can revascularize an area with a perfusion pressure of at least 60 millimeters of mercury higher.

Carter has demonstrated considerable protection against experimental left anterior descending coronary ligation with simple cardiopneumonopexy. However, in the absence of an understandable mechanism by which such protection could have been gained, we regard the effect as due to the incompletely understood benefits which follow nonspecific operative manipulations within the pericardium. It is probable that this is principally due to intercoronary anastomoses, although other possibilities exist.

Bloomer and associates (4) have sought to alter the pressure relationships by ligating the pulmonary arterial supply to the lung segment employed, anticipating that considerable enlargement of the bronchial vasculature would soon raise the pressure in the onlay to a level roughly equivalent to that in the systemic arterial tree. Bloomer and his colleagues (3) have published extensive experimental data indicating that considerable bronchial artery dilatation does, in fact, occur following pulmonary artery ligation. No data on the experimental effectiveness of this method in the prevention of infarction and mortality consequent to experimental left anterior coronary ligations are yet available. It appears that this procedure is at best a rather poor substitute for the direct end-to-end subclavian left lower lobe pulmonary artery anastomosis which we have employed, in terms of the vascularity made available to the myocardium in the lung onlay. On the other hand, it has the virtue of being a less major operative undertaking; and preferable on that score to the one which will be described, provided that the desired ends can be gained. Finally, it appears that success with a direct anastomosis technique would indicate further evaluation of the pulmonary ligation, while failure would signify the impracticality of both. Certainly, the addition of the variation attendant upon bronchial artery dilatation following pulmonary ligation makes that maneuver less attractive experimentally than direct arterial anastomosis.

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OPERATIVE PROCEDURES

Protective operation. The operation has been done (through a left thoracotomy) by dividing the left subclavian artery high in the chest and rotating the proximal end down in order to anastomose it in an end-

to-end fashion with the pulmonary artery to the left lower lobe of the lung. Next, the left anterior two-thirds of the pericardium was excised, the residual interior of the pericardium dusted with talcum powder, and the systemically arterialized lobe swung over and sutured to the edge of the remaining pericardium. The myocardium which lay under the lung onlay had previously been dusted lightly with talcum powder.

When the procedure was complete, the left ventricle and about a third of the right ventricle were surrounded by the lung onlay. The remainder of the ventricular surface was in contact with the residual right posterior third of the pericardium.

Initial attempts at segmental pulmonary resection and epicardiectomy proved impractical owing, respectively, to air leaks in the absence of postoperative water-seal drainage and to an ineffective and spotty removal of the epicardium which appeared to lay the basis for an increased rather than a decreased connective tissue barrier. Talcum dust was, therefore, employed for the stimulation of an initial communicating vascular network of granulation tissue between the onlay and the myocardium.

Eighteen dogs were operated upon as described and survived the initial procedure. The operative mortality rate was 33 per cent. Deaths were due to pneumonia, atelectasis, and fluid in the left side of the chest rather than to anastomotic leaks, any evidence of failure of the left ventricle, or other direct results of the altered physiologic situation. The systemically arterialized segment was never either atelectatic or the site of any significant pneumonia. This observation was in marked contrast to the control dogs in which cardiopneumonopexy without subclavian pulmonary anastomosis had been performed. Water-seal chest drainage would have prevented most, if not all, of the fatalities. In all instances, there was a distinct thrill palpable following the opening of the anastomosis, and the color of the left lower lobe at that time was invariably bright pink.

An identical procedure was done as a control except that the systemic pulmonary shunt was not performed.

The experimental ligation. Many investigators have performed experimental ligations much too early following the protective procedure. An examination of many publications shows that the ligations were carried out 4 to 6 weeks following the initial operation. Therefore, in these studies, an evaluation of the experimental procedure was being made at a time when intercoronary anastomoses have been demonstrated (in Beck's backflow measurements) to remain significantly dilated following nonspecific intrapericardial operations. In effect, therefore, the external manipulation which has been performed on the myocardium or upon its vascular system is given credit for benefits derivative from the widening of the intercoronary vessels—an end result which follows nonspecific trauma to the myocardium, but whose mechanism of production is not yet clear. The same criticism would apply to experimental ligations made prematurely after coronary artery replacement, arterial implantation, and reversal of coronary flow, as well as after one of the various pexies.

With these considerations in view, the experimental ligations were done after an average interval of 20 weeks in the present study. The ligations were performed by opening the previous left thoracotomy incision, separating the dense adhesions between the systemically arterialized lung and the parietal pleura, developing the fissure between the middle and lower lobes, and coming down on the left atrioventricular junction. The left anterior descending coronary artery was isolated in the fat pad which lies just to the left of the pulmonary artery, ligated, and divided. It was deliberately not ligated at its junction with the circumflex artery because the septal branch would then have been inconstantly ligated as well; and it was deemed desirous to avoid the unnecessary variation which would have been so introduced.

TABLE I.—THE RESULTS OF LIGATION OF THE ANTERIOR DESCENDING CORONARY ARTERY IN DOGS WITH CARDIOPNEUMONOPEXY AND SYSTEMIC PULMONARY ARTERIALIZATION

Dog No.	*Interval between original operation and test ligation, wks.*	*Result*	*Remarks*
1	20	Survived	
2	20	Died	
3	16	Survived	
4	24	Survived	
5	10	Survived	
6	20	Survived	
7	12	Survived	
8	16	Died	
9	10	Survived	
10	6	Survived	
11	24	Survived	
12	28	Survived	Died next day of gastric rupture. No change in rhythm
13	52	Died within 20 minutes	The one case with only a few adhesions surrounding the onlay
14	20	Survived	
15	24	Survived	
16	24	Survived	

Mortality rate of ligation of the anterior descending coronary artery in animals with systemic arterialized cardiopneumonopexy, 19 per cent; protection rate, 81 per cent; average interval, 20.4 weeks.

The dogs were observed without any manipulation for 20 minutes following experimental ligation. If they survived this interval, the chest was closed. No dog which survived this period of observation subsequently succumbed. It was necessary to exclude 2 dogs from our experimental series when it was later discovered at sacrifice that a branch rather than the main left anterior descending coronary artery had been ligated.

Final exploration and postmortem examination. An average period of 38 weeks after the experimental ligation, the animals were re-explored through the previous incision, and the status of the pulmonary onlay again assayed. The presence or absence of a thrill was noted, the color of the onlay was described, and the lung-myocardial junction was explored after redevelopment of the middle lower lobe fissure as already described. As the lung onlay was removed from the myocardium, the amount of bleeding was carefully observed, particularly from areas overlying the distribution of the left anterior descending coronary artery.

Following this exploration, the endotracheal tube was clamped and the contents of the thorax were totally removed for examination in the laboratory, and for the preparation of microscopic sections. At this time the condition of the arterial anastomosis, the characteristics of the onlay, the presence and size of any infarctions resulting from the ligation, and the accuracy of the coronary ligation were noted.

In each instance, sections were prepared of the lung onlay, normal lung, myocardium in the distribution of the left anterior descending coronary artery, and of the subclavian pulmonary anastomosis.

Electrocardiographic examinations. An electrocardiogram was made on each dog well after recovery from the initial procedure, and again 1 week following a nonfatal experimental ligation. The preligation examination was generally made 2 weeks prior to the experimental procedure. In addition to the standard leads, AVR, AVL, AVF, and precordial leads were also obtained.

RESULTS

Experimental ligations. Table I summarizes the results obtained when the experimental ligations were carried out. It can be noted that there was an 81 per cent protection rate in these animals, a figure which exceeds the 73 per cent protection rate reported from Beck's laboratory as a result of the Beck I procedures.

One dog which succumbed on the day following ligation has been counted as a survivor since there had been no change in cardiac function and the dog died of a ruptured stomach.

Electrocardiograms. The electrocardiographic data were surprisingly nonspecific. A cardiologist was asked to interpret the tracings made on the animals listed in the tables and the 2 inadvertent "controls" without infarction in which the ligation proved to be of a primary branch of the

left anterior descending coronary artery rather than the primary vessel. In both of these instances he diagnosed infarction; and in 2 dogs with large infarctions the post-infarction tracings were considered less suggestive of infarction than the tracing made prior to ligation! This unreliability of the canine electrocardiogram is confirmed by Wegria, who states that it is due to the instability of the canine mediastinum which permits much greater positional shifting than is possible in the human.

Findings at final exploration and post mortem. These findings are reported in Table II. The dog numbers in this table refer to the same animals as in Table I.

The outstanding fact to be gathered from these data is that in every instance in which the experimental animal survived the ligation, there was an infarction in the distribution of the ligated artery; and in every instance but 2, the infarction was large.

Furthermore, at the time of exploration prior to sacrifice, there was in no instance more than a slow ooze from the lung onlay at the time of its separation from the myocardium. It did not prove practical to measure this flow under conditions simulating the undisturbed situation in the thorax prior to sacrifice because of the unusual circulatory dynamics.[1] There was, however, no doubt at the time of the final exploration that the vascularity in the lung-myocardial interface was minimal.

An important corollary matter was the microscopic examination of the pulmonary vessels in the onlay which had been under direct systemic pressure for a mean interval of 57 weeks. Here inconstant findings were noted—some sections showing advanced pulmonary endarterial hyperplasia, and others exhibiting little if any such changes. It is believed that the absence of these findings in some of the animals must have been caused by a reduction in arterial pressure brought about by the shift in the position

[1]The situation produced by the operation was in reality a rapid turnover side circuit superimposed on the left ventricular output; and the work load of the left ventricle was thereby increased by an undetermined amount.

TABLE II.—INFARCTION SIZE AND INTERVAL BETWEEN LIGATION AND SACRIFICE IN SURVIVORS AT FINAL EXPLORATION AND POST-MORTEM

Dog No.	*Interval, months*	*Infarction size, cm²*
1	7	14
3	7.5	24
4	8	8
5	11	10
6	5.5	12
7	14	8
9	13.5	40
10	13.5	24
11	8	12
14	5.5	12
15	7.5	12
16	Died of overdose of pentobarbital sodium at time of EKG	

Average interval, 9.2 months; average size of infarction, 16 cm.² In all instances the anastomoses were patent, a thrill was present, the lung onlay graft was bright pink, and the bleeding on development of the lung-myocardial interface was minimal.

of the left lower lobe when the cardiopneumonopexy was performed. The arterial pressure in the onlays was invariably sufficient to make them all bright pink; and the pressure also prevented atelectasis even on low endotracheal positive pressure, due to a distention of the alveoli resulting from capillary dilatation. Because of the inconsistency of the microscopic findings, the lobes exhibiting the more advanced changes are accepted as more reliable examples of what systemic artery pressure in the arteries of a lung will produce during this period of time.

Figure 1 is an example of the alterations so induced.

Control animals. It was most difficult to obtain survivors in the control groups, since the new position of the lobe invariably caused atelectasis in the postoperative period. This complication was fatal in 8 of the 10 controls. In the 2 survivors, the most striking difference from the controls was the almost complete absence of adhesions between the onlay and the parietal peritoneum. There was even less vascularity in the lung-myocardial interface than in the experimental series; but the infarction produced in the 1 survivor of ligation was not significantly larger than those seen in the presence of a systemic onlay pressure. This control series is not large enough to permit

FIG. 1. The most severe endarterial hyperplasia brought about by systemic arterialization of the left lower lobe. Most lobes exhibited less of a change. This lobe had been systemically arterialized for 13 months. ×160.

any valid comparison with the experimental series; but the fact that the lungs were atelectatic in this group and not in the experimental series confirms our observation that there was a significant arterial distention of the alveoli in the onlay of the experimental series. The lack of adhesions in the 2 dogs ligated was striking in comparison with the dense adhesions invariably present in the experimental series. However, it would require a much larger number of animals before one could conclude that this would have been a constant finding in the control group.

DISCUSSION

This study would appear to indicate that a juxtaposition of the most vascular tissue onlay possible with the myocardium did not result in a significant vascularization, either through collateral developing prior to experimental ligation of the left anterior descending coronary artery, or by new vessels entering ischemic areas after such interruption. It is sometimes stated that an experimental situation of this sort is not comparable to that which obtains in the clinical circumstance of coronary insufficiency. Then, it is reasoned, adjacent vascularity has an opportunity to replace the primary coronary circulation as it is gradually occluded. There is no doubt that the experimental circumstances here are not strictly comparable to the clinical situation; however, it is difficult to comprehend why vascularization potential should not be apparent in the areas immediately adjacent to the infarction, if not in the infarcted area itself. Certainly, the myocardium of the adjacent areas is ischemic following ligation, for a patchy fibrosis can be demonstrated to surround each area of frank infarction; and a corona of ischemia exists around visibly damaged tissue. One would expect that one could demonstrate a rich ingrowth of vessels from the onlay in response to the needs of the subadjacent tissue in these areas. This has not been observed in our experimental material, nor in others to our knowledge. Also, although the myocardium in the center of the infarction is entirely replaced by connective tissue, the scar tissue also requires blood vessels; and one would expect that these would be most readily supplied by the immediately adjacent onlay rather than from the more distant healthy myocardium. Such is not the case.

Hannon and Baronofsky have recently published interesting data on cardiojejunopexy in which they state that this procedure invoked stable vascular communications of arteriolar size between the intestine and heart. The mortality rate in 19 dogs in which this procedure and anterior descending coronary occlusion had been performed was essentially the same as that reported

for "high pressure" cardiopneumonopexy at 21 per cent (versus 19 per cent in our series); however, the coronary occlusions were done slowly in stages with the help of a Goldblatt clamp. For this reason the considerably smaller percentage of infarctions in their series is not surprising; and the mortality figures are not comparable. It is important to notice that no cardiac difficulty resulted from the occlusion of the superior mesenteric artery in their dogs, and no urokon could be demonstrated in the heart despite good filling of the mesenteric limb supplying the onlay graft. It appears likely that their survivors lived because of the excellent intercoronary anastomoses which were derivative from still patent coronary vessels.

One must conclude that, in our preparation, the interface between the onlay and the myocardium becomes filled with a connective tissue barrier in the immediate postoperative period; and that this barrier prevents effective vascular communication between the coronary and lobar circulatory networks.

If this is so, then how does one explain the remarkably good protection rate which this experimental procedure gave? We believe that this must remain in the realm of speculation at present. Certainly, it was convincingly demonstrated that no vascular protection was offered under these experimental conditions. What alternate mode of protection could there be? It is possible, although it appears unlikely, that the amount of blood available to the ischemic area was sufficient to prevent "mechanism" death (through ventricular fibrillation induced by marked differential oxygenation), but insufficient to prevent infarction. The only other mechanism of which one can conceive is a mechanical one. This has already been suggested by Murray and Allen who postulated that the stabilization of the injured myocardium brought about by various intrapericardial procedures played a significant protective role against coronary occlusion.

It is concluded that "pexies" of various kinds cannot be expected to improve the blood supply to the myocardium significantly, although definite protection may be had by these procedures through other mechanisms such as stabilization of the infarcted myocardium. Retrograde flow studies would have lent additional sophistication to our interpretation of the data; and, in their absence, it remains conceivable that high pressure cardiopneumonopexy did produce some slight increment in total myocardial perfusion. However, since this increase was invariably incapable of preventing infarction upon acute occlusion of the left anterior descending coronary artery, one can presumably conclude that any such increase was inadequate to satisfy the criteria which should attend a successful operation for coronary insufficiency. One need not be hesitant in acknowledging that many facets of this problem remain unquantitated when the ligation of the internal mammary artery in the second interspace frequently will cause a considerable improvement in the symptomatology of patients who are known to have coronary insufficiency!

The absence of any demonstrable alteration in the electrocardiographic tracings despite the production of such large infarctions indicates that electrocardiography cannot be relied upon in determining the presence, size, or location of myocardial infarctions in the dog. It appears that the configuration of the thorax and flexibility of the mediastinum in the dog is responsible for the inaccuracy of the instrument in this species.

CONCLUSIONS

1. Onlay grafts ("pexies") of highly vascular tissue do not revascularize the myocardium to a degree sufficient to prevent infarction.

2. The electrocardiogram is not a reliable diagnostic instrument for the detection of canine myocardial damage, particularly after thoracic surgery.

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EXPERIMENTAL IMPLANTATION OF ARTERIAL HOMOGRAFTS INTO THE VENTRICULAR MYOCARDIUM

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CORONARY ARTERIAL INSUFFICIENCY continues to represent one of the foremost problems in medicine. Many investigators have explored a variety of procedures in an effort significantly to increase the blood supply to the heart. Recently, Smith and associates reported experimental attempts to vascularize the myocardium by the implantation of arterial homografts from the aorta to the left ventricle. They appeared to be encouraged by the results obtained and have employed the method clinically.

In the present study an attempt has been made to determine experimentally the ultimate fate of arterial homografts, as well as prosthetic grafts, with one end anastomosed to the aorta and the other placed into a tunnel in the left ventricle. The results of these studies constitute the basis of this report.

METHOD

Eighteen adult mongrel dogs were used. Ether anesthesia was administered through an endotracheal tube attached to a mechanical respirator. The left side of the chest was entered through the fourth intercostal space, and the thoracic aorta was mobilized for several centimeters distal to the origin of the left subclavian artery. A curved Potts arterial clamp was placed on the aorta at this point with partial occlusion of the lumen. An incision was made into the wall of the aorta, and the end of an aortic homograft (obtained from a donor dog) was sutured to the opening in the descending aorta. The anastomosis was performed with an everting suture of No. 5-0 arterial silk. The pericardium was then opened and a traction suture was placed through the apex of the heart. An Adson clamp was passed from the apex through the mid-thickness of the left ventricle, emerging at the left atrioventricular groove. The free end of the aortic homograft was then ligated, and numerous small perforations were cut into the wall. The end of the vessel was grasped and drawn into place in the ventricular tunnel (Fig. 1). The intercostal and bronchial vessels of the graft were tied in the portion of the graft between the aorta and the heart, while those within the tunnel were left open. The arterial clamp on the aorta was then released and the graft became distended with blood and pulsated actively. In 3 animals a segment of nylon prosthesis of the Edwards-Tapp type was employed instead of a homograft. The pericardium was loosely approximated and the chest was closed in layers. The animals were then observed until death or sacrifice. The hearts were dissected and the grafts injected with sodium iodide. Roentgenograms of the specimens were made.

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RESULTS

Of the 18 animals studied, 9 died within the first 44 days following operation (average of 15 days). The causes of death are shown in Table I. Eight of the implants in this group were homografts and 1 was a nylon prosthesis. At autopsy the graft was patent in 8 animals and thrombosed at the aortic end in 1 (a homograft at 14 days). In the remaining animals the period of observation ranged from 60 to 180 days (average 121 days), and in each instance the graft was either partially or totally thrombosed.

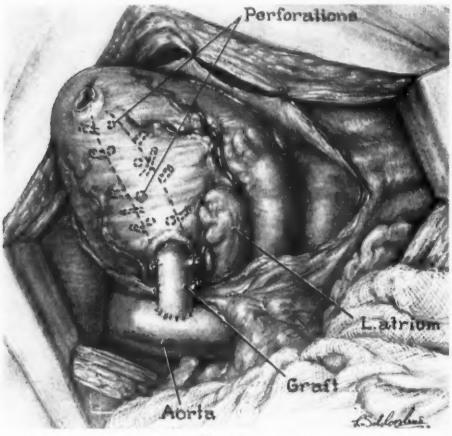

FIG. 1.

FIG. 1. Illustration of arterial homograft anastomosed to the descending thoracic aorta and drawn into a tunnel in the left ventricle. The intercostal and bronchial branches of the aortic homograft remain open in the intramyocardial portion and additional perforations are made. The graft is ligated at its distal end and sutured to the cardiac apex.

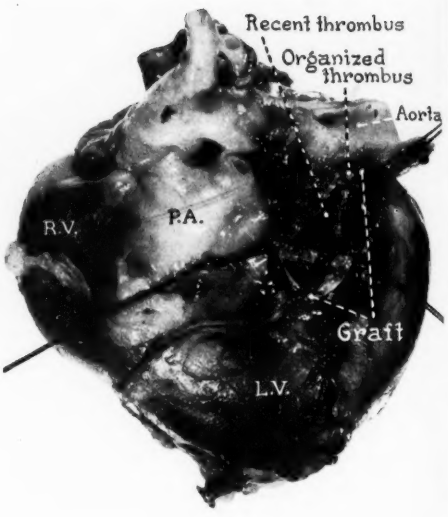

FIG. 2.

FIG. 2. Photograph of an arterial homograft implanted into left ventricle. An organized thrombus is present at the aortic end with more recent thrombosis in the intramyocardial portion.

In 6 of the long term survivors, the thrombosis was found at the aortic end of the graft and involved the entire lumen at that point. In the distal segment of the graft the lumen was found to be partially patent with areas of more recent thrombosis (Fig. 2). In the remaining 3 animals the graft was totally occluded by thrombus from the aorta to the end of the implant in the heart. Of the 2 nylon grafts included in this group, one showed thrombosis at the aortic end with a partially patent lumen distally, and the other showed complete thrombosis. In the 6 animals in which slight patency was present within the intramyocardial portion of the graft, an x-ray film was taken following injection of the implant with sodium iodide. The films obtained failed to demonstrate any communications between the implant and the coronary arteries (Fig. 3).

DISCUSSION

The concept of revascularization of the heart by the implantation of a systemic artery into the ventricular myocardium was first introduced by Vineberg (6). He and his associates have done much experimental work employing the internal mammary artery, and they have shown that the vessel remains patent and develops communications with the coronary arterial circulation. These studies have been extended to include a number of patients in whom they report favorable results (7). Other investigators have reported conflicting findings in similar experimental studies. In our laboratory, implants of vessels considerably larger than the internal mammary artery (common carotid) into the left ventricle were found to remain patent in a high percentage of instances (4). In similar studies on implantation of the carotid artery into the right ventricle, a somewhat lower proportion of the implants remained patent (3). Fuquay and associates also have reported a high incidence of patent intramyocardial implants with the use of a vessel of large diameter (subclavian artery).

TABLE I

No.	Survival, days	Type of graft	Lumen of graft at autopsy	Autopsy
1	11	Homograft	Patent	Purulent pericarditis
2	23	Homograft	Patent	Pneumonia
3	8	Homograft	Patent	Anastomotic leak
4	44	Homograft	Patent	Sacrificed
5	150	Homograft	Thrombus at aortic end; patent at distal end	Sacrificed
6	14	Homograft	Thrombus at aortic end; patent at distal end	Death of undetermined cause
7	78	Nylon	Complete thrombosis	Sacrificed
8	180	Homograft	Thrombus at aortic end; patent at distal end	Sacrificed
9	127	Homograft	Complete thrombosis	Sacrificed
10	180	Nylon	Thrombus at aortic end; slight patency at distal end	Sacrificed
11	60	Homograft	Thrombus at aortic end; slight patency at distal end	Sacrificed
12	4	Homograft	Patent	Empyema
13	24	Nylon	Patent	Empyema
14	70	Homograft	Complete thrombosis	Sacrificed
15	2	Homograft	Patent	Massive atelectasis
16	3	Homograft	Patent	Pneumonia
17	116	Homograft	Thrombosis at aortic end; slight patency at distal end	Sacrificed
18	132	Homograft	Thrombosis at aortic end; slight patency at distal end	Sacrificed

In each of these studies the myocardial implant represented an artery remaining intact at its origin with ligation and division at a point distally. The vessel was then implanted into a tunnel in the ventricular myocardium, and its branches were permitted to remain open. Despite the fact that it is possible to demonstrate prolonged patency of intramyocardial implants of large vessels (carotid and subclavian arteries), these vessels are not as expendable in man as in the experimental animal. In an effort to prepare a similar implant without sacrifice of an important vessel, the suitability of an arterial graft as a substitute has been considered. Smith and associates recently have reported studies concerning arterial homografts and nylon prostheses placed between the aorta and the ventricular myocardium. They conclude that vascular communications develop between such grafts and the coronary circulation.

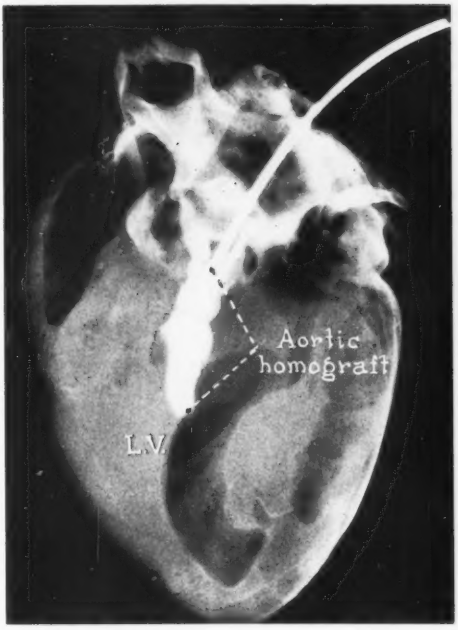

FIG. 3. Injection of patent portion of an intramyocardial graft with sodium iodide. No communications with the coronary arteries are present.

In the studies reported here, it was found that aortic homografts or nylon prostheses remain patent up to a period of 44 days. In animals attended for longer periods, thrombosis of the graft at the aortic end occurred in each instance. In some of the preparations partial patency of the intramyocardial portion of the graft was observed, and in others the thrombosis was complete. Injection of contrast media into the implant failed to demonstrate evidence of communications with the coronary arteries.

SUMMARY

1. In an experimental study implants of arterial homografts and nylon prostheses have been inserted from the aorta to the left ventricular myocardium.

2. These grafts were found to remain patent for a period up to 44 days. In animals observed for longer periods thrombosis occurred.

3. No evidence of the development of arterial communications between the graft and the coronary arteries could be demonstrated.

4. Homografts implanted into the heart appear to behave differently than similar implants in which an intact artery is employed.

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AUSCULTATION AS AN IMPORTANT AID TO THE DIAGNOSIS OF FRACTURES

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ANOTHER CLASSICAL SIGN present in fractures must be added to those stated by Watson-Jones and others. To the list of local swelling, ecchymosis, deformity, crepitus, and local bone tenderness must be added osteophony. This sign, except for crepitus, is the only one which is directly dependent upon the break in the bone, rather than the effect of trauma upon the surrounding soft tissue. Unlike crepitus, or even local bone tenderness, the sign is elicited without manipulation at the fracture site.

METHODS AND MATERIALS

Only a stethoscope and the percussing finger are required for the test. In general, one subcutaneous bony area distal and one proximal to the site of the suspected fracture are selected. With the stethoscope over one site, the other site is tapped with a force similar to that used in percussion of the chest. The sound heard is compared to that heard over an identical area on the opposite extremity. The sites for auscultation and percussion may be distally removed from the fracture by one, two, or more joints. In the case of a fracture, the affected extremity conducts a sound of much less intensity and pitch than that heard on the compared normal side (Fig. 1).

For fractures of the long bones of the upper extremity and of the clavicle, the stethoscope is placed over the manubrium sterni. For the clavicle or the humerus, the olecranon is percussed. To separate a clavicular fracture from a humeral fracture the acromion is tapped while the stethoscope is still on the sternum. For radius or ulna, the corresponding styloid process is percussed while ausculting over the olecranon process or the radial head, or again the sternum may be used.

For the hip, pelvis, femur, tibia, or fibula, the stethoscope is placed on the symphysis pubis. Percussion over the patella will be positive in fractures of the pelvis, hip, or femur. Percussion over the anterior superior iliac spine will be positive only in cases of fracture of the pelvis. For fractures of the tibia or fibula the corresponding malleolus is percussed.

At times, in cases of the tibia and fibula, or the radius or ulna, auscultation and percussion must be done at opposite ends of the same bone. If not, a false negative is elicited because of intact bone conduction over the neighboring bone.

RESULTS

Table I shows results of the test applied to 50 normal patients and to 50 consecutive patients with fractures. In every case of fracture of the long bones, other than the impacted fracture of the head of the femur, in which x-ray examination demonstrated solid cortical contact, the test was positive. In all cases of fracture about the ankle joint the test was negative because of difficulty in applying the test to fragments on either side of the fracture line. In one fractured pelvis the test was negative because of adequate cortical contact of at least one ramus.

DISCUSSION

For some time the phenomenon of alteration in bone conduction following fracture has been known. Its application has been referred to as osteophony by Tillmanns. The basic principle of the sign is the conduction

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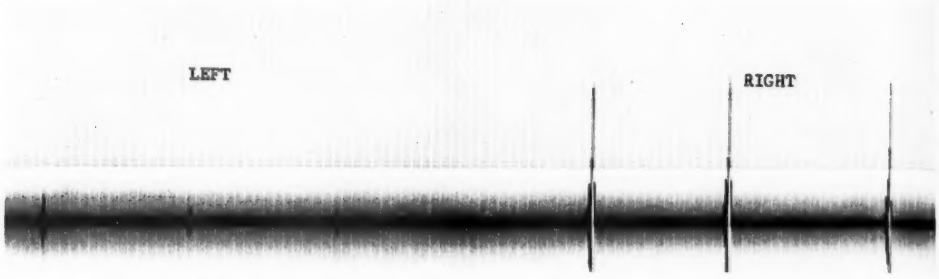

FIG. 1. Phonogram of 69 year old female with intertrochanteric fracture of left hip taken 1 day after trauma. Microphone was applied over symphysis pubis. Percussion of patella on both sides was carried out.

of the sound along intact cortical bone. The conduction can be transmitted satisfactorily across joint surfaces. A complete fracture interrupts this conduction by separation of the cortical surfaces. Therefore, in the case of an impacted abduction fracture of the neck of the femur, with cortical contact, the conduction is normal and the sign is negative. In an impacted fracture of the neck of the humerus, when the shaft is driven into cancellous bone, the conduction is interrupted and the sign is positive.

Because of the difficulty in isolating the distal and proximal subcutaneous bony areas in fractures of the carpal and tarsal bones and the malleoli of the ankle, the sign is not easily applicable.

TABLE I.—RESULTS OF APPLYING TEST TO 50 NORMAL PATIENTS AND TO 50 WITH FRACTURES

Cases tested	*Sign positive*	*Sign negative*	*No. of cases*
Fracture of clavicle	6	0	6
Fracture of humerus	3	0	3
Impacted fracture of the surgical neck of humerus	1	0	1
Fracture of radius and ulna	2	0	2
Fracture-dislocation of shoulder	2	0	2
Fracture of inferior and superior rami of pelvis	3	1	4
Fracture of acetabulum	2	0	2
Impacted fracture of neck of femur	0	1	1
Intertrochanteric fracture of femur	9	0	9
Fracture of femoral shaft	4	0	4
Supracondylar fracture of femur	1	0	1
Compression fracture of lateral tibial plateau	0	1	1
Fracture of tibia and fibula	7	0	7
Fracture of fibular shaft	4	0	4
Fracture of medial malleolus of ankle (tibia)	0	3	3
Total	44	6	50
Cases of NO fracture	0	50	50

Since employing this sign the clinical diagnosis of a fracture has been made when all other physical signs were absent (in the case of a fractured pelvis). The sign was correctly negative in the presence of marked ecchymosis, swelling, local tenderness, and deformity (in the case of a contused leg). Since the test is carried out at a distance from the fracture site, none of these factors influence the results.

The simplicity and rapidity with which this test can be applied, even in the case of an unconscious patient, make it a necessary part of the initial trauma evaluation. The accuracy of this sign suggests that it will be quite useful in times of mass catastrophe, when rapid screening by physical examination will be required.

CONCLUSION AND SUMMARY

A method of bedside diagnosis of fractures by the use of alteration of sound conduction through bone, and requiring the stethoscope as the only instrument, has been presented. Its application in specific fractures has been discussed. Its usefulness in mass catastrophe triage is suggested.

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THE GLANDULAR STRUCTURES OF THE CERVIX UTERI

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SINCE THE EARLIEST DAYS of histology over 100 years ago two concepts have prevailed in describing the epithelial structures of the cervix uteri. The first, still accepted in all modern textbooks, is that they are composed of branching tubular glands of the compound racemose variety. The second, which found several proponents during the middle of the last century, is that the cervical mucosa is thrown up into numerous folds extending in various directions so as to form sinuous pits known as "mucous follicles" or "open glands" in contrast to tubular glands.

This report is based on a study of the cervical mucosa by methods which enabled a three-dimensional reconstruction of the finer epithelial structures. By this means it has been possible to demonstrate that neither of the explanations mentioned are correct or at least complete, and that the basic pattern of the epithelium of the cervical canal is a complex system of clefts with accessory folds and tunnel-like projections.

PROCEDURES

The material for study was obtained by total hysterectomy which had been performed for various pelvic lesions not primarily involving the cervix. In all instances, conventional hematoxylin-eosin microscopic preparations were available, but this report is based on three special procedures: first, a visual inspection of the gross surface markings of the cervical canal; second, examination under a stereoscopic microscope of relatively thick sections of the cervix which had been cleared in xylol and oil of wintergreen; third, plastic reconstructions of the cervical mucosa prepared from serial microscopic sections.

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1. In 41 cases the surface markings of 51 unstained and formalin-fixed strips of the cervical canal 0.5 to 1 centimeter wide and extending from the squamocolumnar junction to the internal os were examined under a stereoscopic microscope at magnifications varying from 7 to 25 or with a simple magnifying glass. By this means it was possible to make sketches or obtain photographs of the so-called plicae palmatae.

2. There were 74 specimens, including those just mentioned, from which 719 thick cleared sections were prepared although some 300 were discarded as unsatisfactory. These sections were cut freehand with a razor blade after the tissue had been fixed in formalin, washed in water, and dehydrated in ethyl alcohol 70, 80, and 95 per cent, and absolute alcohol. After sectioning at thicknesses varying from 0.5 to 2 millimeters they were hydrated by running through the same solutions in the reverse order. The staining was done lightly by immersion in Mayer's hematoxylin 1 per cent. The fixation and clearing were then accomplished by placing the sections for from 24 to 48 hours in ethyl alcohol 70, 80, and 95 per cent, absolute alcohol, xylol, and oil of wintergreen. They were kept in mineral oil and also examined in oil under a stereoscopic microscope.

3. Nine series of serial sections, totalling over 2,500 preparations, were made from 6 additional specimens. They were chosen to include both nulligravidas and women who had borne children, and the ages of the patients were 27, 30, 36, 43, 49, and 51 years. The details of this part of the study have been reported by Fluhmann and Dickmann (2). The tissues were embedded in paraffin and the serial sections were cut at a thickness of 8 microns and stained with hematoxylin-eosin. Either drawings with a microprojector or photomicrographs were made of every

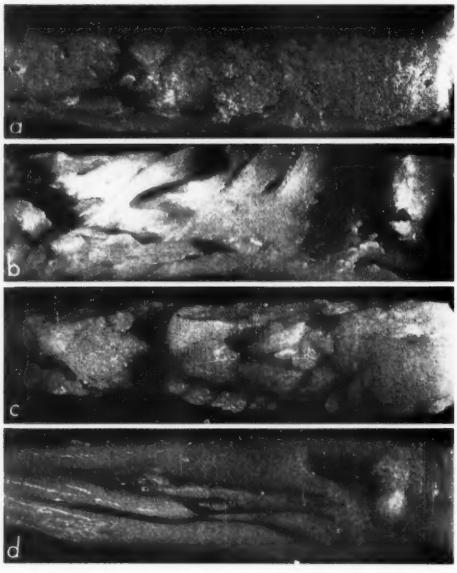

FIG. 1. Surface markings, or so-called plicae palmatae, of the cervical canal. There is no recognizable attempt at a pattern of arborization. The external os is to the right. The faint vertical lines in the upper right corner of "d" are due to surgical clamp. a and b, Patient aged 54 years, gravida 1, para 1; c, patient aged 51 years, gravida 2, para 2; d, patient aged 32 years, gravida 4, para 3. ×2.8.

second or fourth section. Outlines of the epithelial structures in these sections were then copied with India ink on rectangular sheets 5 by 7 inches and 0.030 inch thick of a clear plastic material (cellulose acetate). When these sheets with the tracings were superimposed a transparent plastic reconstruction was obtained which presented to view the course of the various epithelial formations of the cervical mucosa.

SURFACE MARKINGS OF THE CERVICAL CANAL

The grossly visible folds of the cervical mucosa have held little interest in recent years, but when mentioned in current textbooks they receive the classic description which has been in vogue for over 100 years. They are known as the "plicae palmatae" and are stated to consist of from 1 to 4 longitudinal folds or rugae from which emanate smaller accessory folds directed obliquely toward the internal os. Their general pattern is said to resemble the trunk and branches of a tree and hence they also acquired the name of "arbor vitae." Some of the older authors attributed considerable importance to these folds because they were supposed to allow for the stretching of the mucosa which accompanies the dilatation of the cervix during labor. Tyler Smith in 1855, for example, wrote that "another purpose served by the reduplications of the mucous membrane of the cervix uteri is . . . the dilatation of the cervix uteri during labor, without laceration. In pregnancy, the cervix uteri is enlarged and unfolded considerably by the processes of growth, and in this enlargement the rugae take part; but nevertheless, at the time of parturition, a large amount of distension takes place during the passage of the fetus. Without some such provision as that offered by the rugae of the cervix, laceration of the mucous membrane would be a frequent occurrence."

The folds have their origin in embryonic life and at first they also involve the body of the uterus. In time, however, they become limited to the cervical canal and Hunter has described the appearance of longitudinal and transverse folds forming broad swellings which project into and fill the lumen of the cervix. In an effort to accommodate themselves in the available space they assume an oblique direction and Hunter believed that they are the forerunners of the plicae palmatae. They are well developed in the 160 millimeter fetus.

Since the present study shows that basically the cervical mucosa is composed of innumerable clefts the grossly visible plicae palmatae bear a close relationship to this construction. The folds serve to form grooves which extend through the depth of the mucosa either as single structures or as more extensive depressions from which originate finer clefts.

However, examination of 51 specimens of the cervical canal indicates that a regular pattern of arborization is nonexistent. There

is a great dissimilarity in the configuration of the folds and grooves and no consistent arrangement could be determined. The accompanying photographs (Figs. 1 and 2) demonstrate this divergence. In the first place it is noted that the grooves vary in length, width, and depth. They may extend for as little as fractions of a millimeter to as much as 1.5 centimeters, as in the longitudinal grooves in Figure 1d. In width they may merely be of microscopic dimensions or measure up to 1 millimeter as in the pronounced divisions between the transverse folds in Figure 2c. Their depth was determined from microscopic sections and reached a maximum of approximately 3 millimeters, namely the depth of the whole mucosa.

The inconsistency of the pattern of the folds and grooves is illustrated in Figures 1 and 2. In some cases, as in Figure 1a and b, the surface is quite smooth and there are only very faint shallow grooves or small depressions. Others, as in Figures 1b and c and 2d, are very pronounced oval or globular projections with deep irregular pits between them. Some attempt at regularity is seen in Figure 2c where there are deep transverse clefts and Figure 1d with less marked longitudinal markings, but these types are unusual. Especially noteworthy are circular or oval pits of varying size, and in Figures 1b and c one is struck by the appearance which suggests the existence of broad-based polypoid protrusions. Although at times, as in Figure 2d, there is a relatively large pit from which arise a number of irregular grooves, it is significant that each fold or cleft is an independent unit and there is no uniform branching or attempt at any sort of communal arrangement.

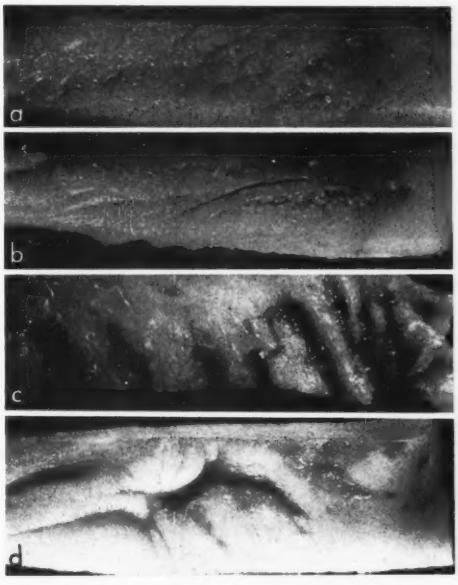

FIG. 2. Surface markings, or so-called plicae palmatae, of the cervical canal. The external os is to the right. a, Patient aged 49 years, gravida 2, para 1; b, aged 30 years, gravida 2, para 2; c, aged 43 years, nulligravida; d, aged 27 years, gravida 4, para 4. ×2.8.

SIMPLE AND COMPOUND CLEFTS

The thick cleared specimens and the reconstructions on sheets of cellulose acetate allow a three-dimensional view of the epithelial structures of the cervix uteri. They clearly demonstrate that there are no tubular glands which descend from the surface and divide in a compound racemose manner. On the contrary, the large numbers of tubular structures which appear in almost all isolated sections of the cervical mucosa are seen to be segments of irregular passages or tunnels which run a course more or less parallel to the surface. They end blindly at one extremity and their origin can be traced to a cleft or groove which pierces the surface mucosa.

The basic structure of the cervical epithelium consequently is not a tubular gland originating at the surface but a cleft or groove (Figs. 3, 4, and 5). These clefts vary greatly in size and complexity. Some are simple crevices in the cervical mucosa, but the majority have complicated characteristics and may be termed "compound clefts." The more pronounced correspond to the grooves between the plicae palmatae but many finer clefts arise from them. They extend in longitudinal, transverse, and oblique directions in regard to the cervical canal but

FIG. 3. Thick cleared section of cervix uteri, illustrating a series of deep clefts with accessory folds, lateral extensions, and associated tunnels. The two clefts to the left show union of opposing walls with partial obliteration, a process which may be involved in the formation of tunnels. The surface presents many papillary protrusions. From a patient aged 36 years, gravida 1, para 1; pregnancy 14 years ago; hysterectomy for uterine myomas and adenomyosis. Photograph taken with section immersed in mineral oil. ×5.4.

the transverse seem to predominate. They may penetrate the whole depth of the mucosa for a distance of 3 millimeters, but many are more superficial. The smaller clefts originate either from the grooves between the plicae or from the surface and may vary from 100 microns to 1 or more millimeters in length and from 30 to 70 microns in width. Each cleft is an independent unit and although they run in all directions they do not cross one another nor do they divide in their linear course.

The compound clefts present many complicated features, but these may be simplified for purposes of description. Although almost all present a single crevice occasionally a cleft may bifurcate and continue downward as two branches. The walls are very irregular and present numerous folds and papillary projections. These protrusions are not only seen at the surface (Fig. 3), but may appear at lower levels in the deeper structures. They themselves are strong evidence in favor of clefts as it seems unlikely that they would develop in narrow tubular glands. Just as the deeper grooves between the plicae give rise to finer clefts, many of the clefts themselves are extended laterally by accessory clefts. These secondary formations are almost always smaller than the primary clefts but since they are also subject to the same variations they add greatly to the complexity.

The most striking features of the compound clefts are the tubular tunnels or passages. These structures are very numerous and in a single section of the cervical mucosa they may cover a whole microscopic field and no opening to the surface is apparent. However, their connection with a cleft always can be demonstrated provided a sufficient number of serial sections is followed. The tunnels extend in a more or less straight line, and in only one of two directions, that is, either downward or longitudinally in the same lineal course as the cleft of their origin. In the latter case they are parallel to the surface although obviously at different levels (Figs. 3, 4, and 5).

The majority of the tunnels arise from one or both extremities of the compound clefts and may be compared to the extended fingers of the hand. Often only 1 or 2 protrude but there may be as many as 12 or more from a single cleft. The individual tunnels themselves never divide into distinct branches as with compound racemose glands.

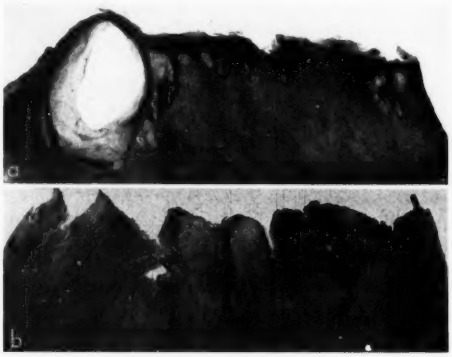

FIG. 4. Thick cleared sections of cervix uteri. a, Chiefly tubular tunnels parallel to the surface. b, Several clefts with characteristics mentioned in legend of Figure 3. Photograph taken with section immersed in mineral oil. a, From a patient aged 44 years; nulligravida; hysterectomy for uterine myomas. b, From a patient aged 42 years; nulligravida; hysterectomy for uterine myomas. ×3.1.

The accessory clefts also may give rise to tunnels which may be seen running alongside or beneath the primary cleft. The tunnels vary greatly in outline and dimensions. They may be small circular tubes or larger indented and irregular oval and elongated structures. They may be so short as to be merely a small pouch but at times they are even longer than the cleft of their origin. They all end blindly and it is likely that when their source at a cleft becomes closed they give rise to nabothian follicles. This theory is supported by the fact that in a number of instances of relatively long distended tubes both ends were closed and the lining consisted of flattened low cuboidal epithelium.

The main features of the clefts may be demonstrated by the use of the outline tracings of the serial sections which were used in making the plastic reconstructions. Figure 6 was prepared employing every eighth section so that the distance between each drawing is 64 microns, from outline 1 to 12 it is 768 microns, while the width of each drawing is of 310 microns. The area represents the side of a plical fold and to the left of each outline is a deeper groove which was grossly visible. The clefts are directed obliquely downward, and are relatively small, for example *D* in outline 2 measures only 220 microns in depth. Seven clefts, labeled *A* to *G*, are shown, but *A* is near the edge and is not complete. Clefts *E*, *F*, and *G* are very small and merely represent small grooves which terminate in small tunnels under the surface. For instance, *G* is seen as a small cleft in outlines 9 and 10 but in the preceding 6, 7, and 8 it appears as a small tubular extension. Cleft *B* is seen in all 12 sections and shows an irregular outline with accessory folds but in this case there are no tunnels arising from it. This cleft was followed for 136 sections, namely, for over 1 millimeter in length. The structure *C* is of approximately the same length but in outlines 1 to 8 it appears merely as a number of irregular tubular passages which are parallel to the surface and the cleft opening is seen from 9 to 12. Cleft *D* is of interest in view of the many tunnels with which it is associated. The open cleft is visible in outlines 1 to 9, but in the latter there is a mere dent in the surface and below this there are 12 or more tunnels of varying size which diminish in number in the succeeding outlines 10 to 12.

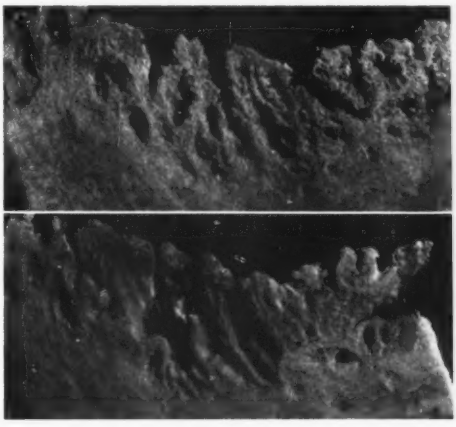

FIG. 5. Thick cleared sections of cervix uteri, illustrating irregular clefts and tunnel-like passages. Photographs taken in air and with direct illumination. Autopsy specimen from a woman aged 24 years with chorioepithelioma uteri and generalized metastases, and who had been treated with daily massive doses of stilbestrol. ×3.1.

In preparing the outline drawings for Figure 6 at this magnification it was necessary to use relatively thick lines so that the details of the epithelial lining could not be shown. They are, however, demonstrated in the 2 photomicrographs of Figure 7 which were used for plastic reconstruction.

Figure 8 is reproduced in order to show the appearance of the clefts when sections cut parallel to the surface were employed. This photomicrograph is of the one hundredth section down from the surface. Figure 9 presents 3 interesting photomicrographs which were employed for making a plastic reconstruction of the epithelial structures of the cervical mucosa. It demonstrates that although a single section (in this case there were 16 such consecutive preparations) may have the appearance of numerous gland-like structures formerly interpreted as compound

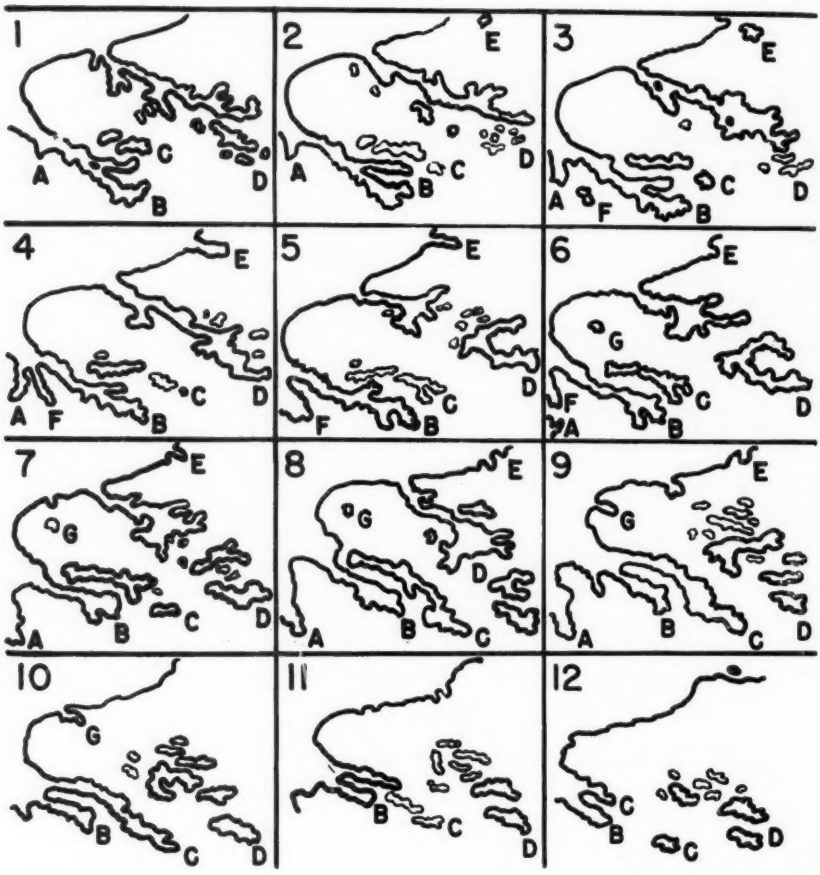

FIG. 6. Tracings of epithelial structures made from photographs of serial sections of the cervix uteri. Each outline represents every eighth section. The distance between each outline is consequently 64 microns, and from 1 to 12 it is 768 microns. From a patient aged 27 years, gravida 4, para 4; hysterectomy for chronic salpingitis with hematosalpinx. Reduced 4/7 from a magnification of 22.5.

racemose glands they can be traced to actual clefts if a sufficient number of serial sections is followed.

THE MORPHOGENESIS OF THE CERVICAL CLEFTS

A consideration of the origin of the clefts and tunnels suggests two possibilities. The first, which undoubtedly will appeal to our habit of associating the cervix with tubular glands, is that they result from invaginations of the epithelium. In other words, the clefts of the cervix gradually evolve from small depressions which burrow into the stroma somewhat as do the glands of the endometrium.

The second possibility, which I should like to emphasize, is that the clefts do not develop from invaginations but from a complicated process of exophytic growth. In this case attention is not directed to the grooves but to the folds of the epithelium and stroma which form their walls. The behavior of the cervical epithelium during fetal life, in the newborn, and in children up to the age of the menarche strongly supports this thesis.

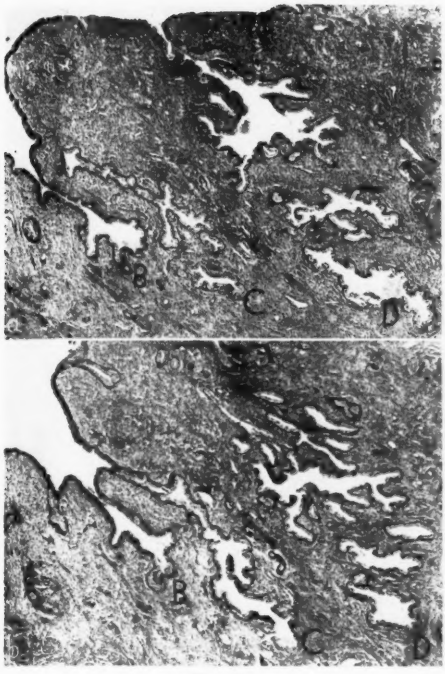

FIG. 7.

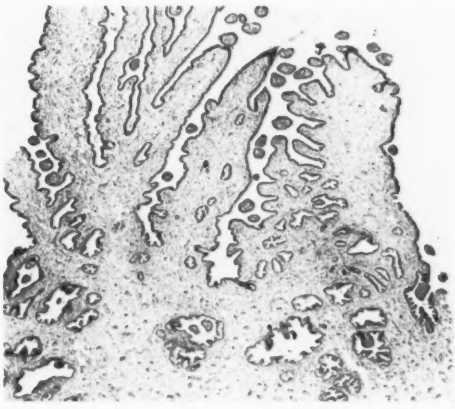

FIG. 8.

FIG. 7. Two of the photomicrographs used to prepare outlines reproduced in Figure 6. a, Original for tracing 7 and, b, for tracing 9 in Figure 6. The lettering *B*, *C*, and *D* is for the corresponding cleft structures. ×23.

FIG. 8. Photograph from a series of horizontal sections of the cervical mucosa. It is the one hundredth section (800 microns) from the surface, and illustrates a number of clefts with folds and papillary outgrowths. The isolated gland-like structures actually are "tunnels" and all could be traced to the clefts at various levels. Patient aged 30 years, gravida 2, para 2; hysterectomy for irregular uterine bleeding for which no histopathologic explanation was found. ×15.9.

The embryologists have described the appearance in very young embryos of longitudinal folds of the epithelium which at first involve both the corpus and the cervix. In time they become limited to the cervix and both transverse and oblique folds are added to the longitudinal. Hunter considered them as forerunners of the plicae palmatae, and it seems likely that they also are the precursors of the cleft system of the finer glandular structures. I have previously shown (1) that the formation of these folds is well advanced in the fetus during the third trimester of pregnancy. In the later weeks of intrauterine life a secondary growth of the cervical mucosa is superimposed on this system of folds and grooves and its maximal intensity is reached in the newborn at term. This process is a response to endocrine stimulation and one of its characteristics is a great proliferation of the epithelial cells so that as they increase in number they are thrown up into innumerable small protuberances varying from minute projections to actual papillae, folds, and finger-like processes. With the birth of the baby and the disappearance of the maternal hormones there is a regression of the cells but the major mucosal folds persist and they are accompanied to a greater or lesser extent by the secondary folds and papillary outgrowths.

This system of folds with their accessory outgrowths offers a valid explanation for the original production of the clefts characteristic of the adult cervix, and the process no doubt is intensified with the increased hormonal activity of the menarche and the early years of menstrual life. It now becomes necessary to explain the mechanism which produces the tubular tunnels or passages and in this connection it is important to point out that these do not appear until the age of the menarche. It seems very likely that the

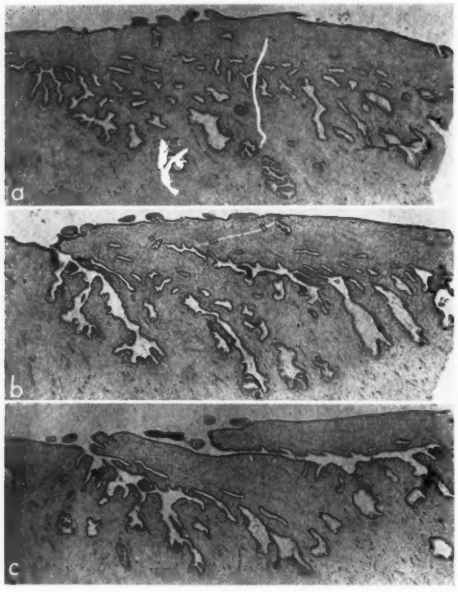

FIG. 9. Three photomicrographs of serial sections of the cervical mucosa 24 sections (192 microns) apart. a, Large numbers of irregular structures which formerly were interpreted as segments of curved and branching tubular glands extending down from the surface. Actually, however, they run lengthwise more or less parallel to the surface. b and c, Demonstrate that they originate from 2 compound clefts which in this case pierce the mucosa in an oblique direction. The 2 clefts are visible in 124 sections, a distance of almost 1 millimeter. The appearance of "tunnels" in "a" is present in 16 sections (108 microns) of the structure on the left, while similar structures seen in "a" and "b" of the cleft on the right are found in 56 sections (448 microns). Attention is also directed to the papillary projections and folds at the surface in the 3 photographs and within the cleft on the left in "c." ×12.75.

clefts with their irregular folds and outgrowths undergo a process by which opposing walls become adherent and that the tunnels result from this partial obliteration (Fig. 3). The close relationship between tunnels and clefts strongly suggests that at one time they form part of the same structure. This is seen in the direction which the tunnels assume for they are always found following the same linear course as the clefts of their origin, and they do not branch. Also impressive is a frequent finding, for example cleft *D* in Figure 6, 5 to 9, and *C* in Figure 6, 11 and 12, where the cleft becomes reduced to a mere indentation at the surface while the tunnels run parallel and directly below. It is probable that further light on this aspect of the problem will come when changes of the maternal cervix in pregnancy also have been studied by three-dimensional methods.

DISCUSSION

It is not likely that the acceptance of simple and compound clefts in lieu of tubular racemose glands as the basis of the glandular structure of the cervical mucosa will affect our fundamental concepts of disease of the cervix uteri. Yet, it does have a direct bearing on our further understanding of at least four phases of gynecologic pathology.

1. In the first place, it emphasizes the differences between the epithelium of the endocervix and the endometrium, both as to their development and anatomy.

The endometrium in the newborn child is composed of cuboidal cells and the glands-to-be are represented by small invaginations of the surface. The cells themselves are completely devoid of secretory activity as evidenced by a lack of staining with periodic acid leucofuchsin. The cervical epithelium at this age, on the other hand, shows tremendous proliferative and secretory activity. The cells are of a high columnar type, filled with a secretion which takes special stains, and there is a marked production of complicated folds and accessory outgrowths.

In the adult, the endometrium has become a highly specialized tissue with characteristic tubular glands and a stroma which responds to stimulation by the ovarian hormones during the varying phases of the menstrual cycle. The glands are lined by columnar cells distinct from those of the surface. The endocervical mucosa, however, does not have specialized tubular glands, but it is composed of innumerable small and larger clefts with their characteristic accessory folds, papillary outgrowths, and tunnel-like protrusions. These, moreover, are lined by a columnar epithelium with the same

histologic characters and potentialities as the surface cells of the cervical canal. This observation was made many years ago and led Pouchet and Tourneux to speak of "diverticula" of the cervical epithelium when discussing the plicae palmatae and the so-called "open glands" of those days.

The possibility of an embryonic origin for the cervical mucosa distinct from a muellerian source must be kept in mind. The behavior of this tissue in many ways is more like that of the vagina than of the endometrium. Robert Meyer, moreover, definitely showed that at one stage urogenital cells invade not only the vagina but most of the cervical canal. We also cannot help but believe that the picture of the clefts with their accessory folds and tunnels is much more reminiscent of the paraurethral glands described by Huffman than of any endometrial formation.

2. Several attempts to determine cyclic changes in the cervical "glands" have been made but with contradictory results. Since the clefts must be an essentially permanent anatomic system it seems that such modifications under endocrine stimulus are improbable. Any cyclic variations must appear just as readily in the surface epithelium as in the deep structures which have the same histologic properties.

3. Although the cervix uteri has been grouped as a glandular organ, it has seemed remarkable that only some 5 per cent of its cancers are of an adenomatous type. The fact that the cervix does *not* have tubular glands in its normal make-up gives a ready explanation for this incidence, and the origin of adenocarcinoma of the cervix must be explained on some other basis.

4. The finding that the normal structures of the cervical mucosa probably result from a basic property of this tissue to develop outgrowths is significant in the light of its common pathologic changes. As the epithelial cells proliferate, they are no longer contained in a straight line but force themselves outward to form folds and papilla-like protrusions. This process is quite likely a characteristic of urogenital derivatives and I have been able to reproduce such growths in the vaginas of rats treated for long periods of time with a mixture containing estrogen, progesterone, and testosterone. In the human cervix the same pathologic exophytic process is constantly observed in granular or papillary erosions and polyps and is probably the basis for the epithelial proliferation characteristic of normal gestation.

CONCLUSIONS

The plicae palmatae of the cervix uteri do not show a regular pattern of arborization. The folds run in longitudinal, transverse, and oblique directions and form a very irregular arrangement of grooves which may penetrate the whole thickness of the mucosa.

The basic pattern of the epithelium of the cervix uteri is of multiple grooves formed by the plical folds and of innumerable finer irregular clefts arising from them. The tubular structures formerly described as glands descending from the surface and dividing into irregular branches actually are straight tunnels which course parallel to the surface and originate from the extremities or the lower limits of the clefts.

It is suggested that this system of compound clefts is derived from epithelial folds which first appear in the embryo and that they represent a fundamental property of the cervical mucosa to undergo exophytic proliferation.

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SIMPLE EXCISION OF THE UNATTACHED LAMINA FOR SPONDYLOLYSIS

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IN SPONDYLOLYSIS and spondylolisthesis there is increasing evidence that the backache and leg pain are due not to instability of the lumbosacral joint as has been generally believed, but to the abnormal mobility of the unattached lamina. For this reason, the removal of the unattached lamina is beginning to replace the various techniques of spinal fusion in the treatment of this condition.

The term "spondylolysis" in its broadest sense infers a dissolution of any part of a vertebra, but common usage has restricted the term to a defect in the isthmus or pars interarticularis (Fig. 1). The term is a poor one since the bony defect undoubtedly is due to aplasia rather than to dissolution. Spondylolisthesis is spondylolysis in which, as a result of the lack of anchorage normally supplied by the inferior facets, there is a forward displacement of the body of the defective vertebra on that of the one below. Prespondylolisthesis has been used by a few authors to describe spondylolysis, but such a label is unwarranted since vertebral body displacement is not an invariable or even a prevailing consequence of the osseous defect. There is much unsubstantiated speculation in this respect, yet it is the exception rather than the rule to observe progressive displacement, regardless of whether displacement already has been demonstrated. Friberg in a study of 142 conservatively managed spondylolisthetic patients found minimal further tilting or slipping in only 10 cases, and there was no correlation between this movement and the symptoms. He found the functional results in 44 fused cases only slightly better than those in the conservatively managed series.

In the absence of forward slipping (olisthesis) the diagnosis frequently is overlooked since the isthmus defect usually is not apparent in standard anteroposterior and lateral roentgenograms of the lumbosacral spine. When oblique views are made, spondylolysis emerges as a significant entity in the differential diagnosis of low-back pain and sciatica. The incidence of the bony defect, without regard to symptoms, was studied by Willis. In examining 1,520 human skeletons he found a pars interarticularis defect in 5.09 per cent.

LITERATURE

In 1880 Neugebauer in his classic presentation of 101 cases of spondylolisthesis described the defect of the lamina and postulated that it may be due to defective ossification or to primary fracture of the pars interarticularis. These hypotheses became the subject of rather heated discussion by Lambl (1885), his former professor, who formulated the theory that "primary hydrorrhachis" was the etiologic factor, and by Herrgott in 1883 who contended that inflammatory changes secondary to trauma resulted in the solution of bony continuity. Controversy on the subject has periodically erupted in the literature ever since. It is not the purpose of this communication to consider the matter of pathogenesis but it seems significant that this defect is largely confined to the vertebra that is commonly

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the seat of congenital anomalies such as spina bifida occulta.

In 1931 Chandler reported 18 cases of spondylolysis. All patients had been examined because of low-back pain with or without associated leg pain. Olisthesis was present in 11 cases. There was no apparent relationship between the presence or degree of displacement and the symptoms. He concluded that the stability and strength of the lumbosacral articulation are impaired by the presence of such defects but did not describe the mechanism for production of symptoms.

It remained for Kleinberg in 1939 to direct attention to the precise site of the pathologic condition responsible for symptoms in most cases. He pointed out that the laminar defect in spondylolysis of the fourth or fifth lumbar vertebra is close enough to the sciatic nerve so that when the connective tissue that bridges the bony hiatus is subjected to an injury the resultant hemorrhage and edema may extend to and irritate the nerve.

Caldwell in 1944 advocated exploration and decompression of the nerve root in spondylolisthesis with sciatica, and suggested that removal of the unattached lamina with its inferior articulating processes might in certain cases be all that is required.

Out of these significant musings, there evolved a clearer concept of the pathologic entities involved and the mechanisms by which symptoms develop. The investigations of Briggs and Keats (1947) lent confirmation to previous speculation. They found that the irritative focus lay along the course of the nerve root as it curves around the medial and inferior aspect of the pedicle of the involved vertebra to pass through the intervertebral foramen. They recognized the necessity for complete removal of the unattached lamina and its pseudoarthrosis consisting of a poorly defined fibrocartilaginous mass that merges with the surrounding ligaments and compromises in varying degrees the underlying nerve root. In cases of leg pain they advocated unroofing the foramen and carefully exploring the nerve roots laterally. Their operation was completed with a standard bonechip fusion in all 18 cases presented. This work is a significant contribution in the long quest for a solution to this problem.

FIG. 1. A surgically removed specimen (Case 5) beside a normal vertebra; line indicates the location of the bony defect.

Adkins (1955) described from his own operative experience the normal and pathologic relationships of the structures involved in spondylolisthesis. Three of his patients, because of advanced age, were treated by simple decompression without any attempt at fusion. Relief was immediate and complete in each case, but he was appalled by further slipping in 1 instance although there were no associated symptoms. Adkins postulated that postoperative recurrence of leg pain may be caused by involvement of the nerve root in the dense fibrosis that follows an extensive operation within the spinal canal, and acknowledged that this, of course, would not be affected by local arthrodesis of the spine. His observations suggest that the solution of the problem of recurrent leg pain is more likely to lie in the direction of effective methods of preventing or reversing the process of fibrous tissue formation than in the perfection of a fusion technique.

TABLE I.—DATA ON 15 PATIENTS WHO UNDERWENT OPERATION FOR SPONDYLOLYSIS

Case No.	*Sex*	*Age, yrs.*	*Employment*	*Level of defect*	*Olisthesis, grade*	*Date of operation*	*Days in hospital after operation*	*Results*
1	M	28	Laborer	L5	0	6-29-54	9	Good
2	M	39	Carpenter	L5	I	8-10-54	10	Excellent
3	M	49	Salesman	L5	I	10- 1-54	10	Excellent
4	F	34	Housewife	L5	0	10- 7-54	11	Fair
5	F	43	Housewife	L5	0	10-15-54	8	Excellent
6	F	37	Schoolteacher	L5	II	11-17-54	10	Fair
7	M	50	Broker	L5	I	11-22-54	14	Excellent
8	F	50	Housewife	L5	II	4- 7-55	15	Good
9	M	49	Factory foreman	L5	I	5- 4-55	10	Good
10	F	37	Housewife	L5	I	6- 1-55	28	Excellent
11	M	59	Electrician	L5	II	6- 2-55	9	Fair
12	F	29	Housewife	L5	0	8-15-55	10	Excellent
13	M	60	Executive	L4	I	8-29-55	9	Good
14	M	37	Machinist	L5	I	9- 7-55	9	Excellent
15	F	56	Rooming house	L5	II	10-11-55	9	Poor

The fifth lumbar vertebrae were transitional in Cases 2 and 5, and in both instances spina bifida occulta was present. In Case 5 the isthmus defect was unilateral. Spina bifida occulta also was present in the fifth lumbar vertebra in Case 9, and, without apparent relation to symptoms, in the first sacral vertebra in Cases 1 and 6.

Woolsey in 1954 and Gill, Manning, and White in 1955, in concurrent independent investigations, questioned the rationale of the concept of instability at the lumbosacral junction as the cause of the symptoms. They wondered at the persistent insinuations of significant progressive slipping in adults having spondylolysis, despite documentary evidence to the contrary. They supplanted the prevailing concepts of the mechanism of symptoms with their own which were based on their observations made during operation. They attributed low-back distress to traction on surrounding ligaments and dura by movement of the loose lamina; and radiation of pain to the leg to direct pressure on the nerve root by the fibrocartilaginous mass that invariably surrounds the false joint. In some cases rocking of the unstable lamina was observed to exert traction on nerve roots passing to the lower vertebral level. To support their views, these investigators described favorable results in series of cases in which the operation consisted of simple removal of the unattached lamina and decompression of the nerve roots. Gill and his associates mentioned spinal fusion only to condemn it as an unnecessary and often complicating procedure.

In view of the steadily accumulating evidence that the symptoms are due to the false joint at the bony defect we agree that it does not seem reasonable therapy to insert a bone graft that may serve to superimpose one pseudoarthrosis on another.

PATHOLOGIC ANATOMY

In all patients upon whom we have operated for spondylolysis, there has been a poorly delimited fibrocartilaginous mass surrounding the pseudoarthrosis. In no instance was the unattached lamina proved to be in direct contact with the nerve root. Such contact appeared to be prevented by a shelf of bone projecting caudally from the pedicle and partially covering the nerve root as it passed about the base of the pedicle. Since the nerve root is not well disclosed until after the unattached lamina and this bony shelf have been removed, we were unable to ascertain the exact mechanism of pain production. A bony spur on the posterior inferior margin of the body of the vertebra occasionally was found to be in contact with the nerve root where it rounded the pedicle to pass through the foramen. Forward displacement of the inferior articulating process, or surrounding tissue reaction from increased motility at this site never was demonstrated by us to have compressed the underlying nerve roots.

Gill and associates ascribed the occurrence of coccygodynia to adhesions between

the dura and the ligamentum flavum. One of our patients had this condition and it was relieved by the operation that included the removal of the ligamentum flavum.

The pathologic findings were identical in 3 cases in which occult spina bifida was present in addition to the isthmus defect. There was no essential difference in the symptoms in cases of spondylolysis and those in which displacement of the body was present. This fact together with the relief afforded by simple removal of the unattached lamina indicates that displacement of the body is not the cause of the symptoms.

OPERATION

The essential feature of the operation is the complete removal of the unattached lamina, the ligamentum flavum, and the mass of tissue surrounding the pseudoarthrosis. This procedure necessitates a wide lateral exposure. The nerve roots are disclosed by removal, by means of a small electric drill, of the shelflike projection from the pedicle. This shelf invariably covers the roots at least partially, and seemingly protects them from compression by the unattached lamina. Examination of the involved disk, in no instance, disclosed a significant degree of protrusion. In 2 instances in which olisthesis was present, an interbody fusion was attempted (Cases 2 and 10). No rationale is offered for this adjunctive measure. It was proposed on a purely empiric basis. Roentgenograms revealed posterior migration of the bone grafts in Case 10, necessitating their removal 7 days after the original operation. Both patients have had excellent results. For purposes of study, several defective laminae were excised intact (Fig. 2).

RESULTS

The criterion for surgical intervention in spondylolysis, with or without olisthesis, is incapacitating pain. Patients with moderate distress may eventually come to operation but certainly should not unless conservative measures have proved ineffective. We have

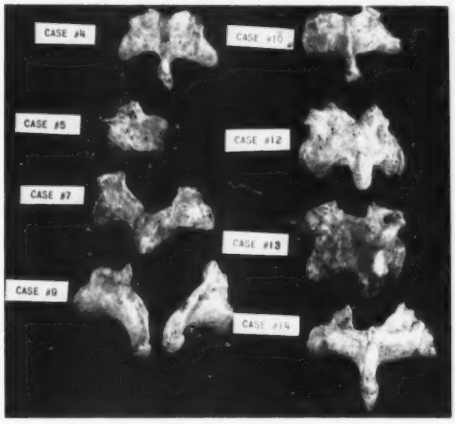

FIG. 2. Unattached laminae removed intact.

operated upon 15 patients who have been postoperatively followed for periods of from 20 to 36 months. The results have proved surprisingly good. A synopsis of the data of each case is given in Table I.

Clinically, no pathognomonic syndrome has evolved and the differential diagnosis is based on roentgen findings. With 1 exception (Case 7) all patients complained of leg pain in addition to backache. Duration of symptoms ranged from 2 months to 28 years with an average of 7 years and 4 months. Neurologic findings were variable, ranging from obvious signs of nerve root compression to no demonstrable deficit.

The operative results were as follows: excellent, unrestricted activity with no backache or leg pain, in 7 cases; good, unrestricted activity with occasional mild backache or leg pain, in 4; fair, unrestricted or slightly limited activity with recurrent mild backache or leg pain, in 3; poor, persistent backache or leg pain, in 1 case.

In the 1 case (Case 15) classified as a poor result there are no physical findings, and in the 20 months that have elapsed since her operation it has become obvious that this patient enjoys an audience for the recital of her symptoms. She maintains that she must be on her feet 18 to 20 hours a day caring for a 17 room boarding house,

nursing a patient with cardiac disease, and in addition, sewing for her grandchildren. On a recent follow-up visit she had just returned from a 5 day, 2,000 mile automobile trip which she enjoyed immensely, and during which she had no backache and was able to outwalk her younger sister. This case constitutes an object lesson that one should not too readily ascribe symptoms to a defect disclosed by roentgenography.

In Case 10 the hospital stay was prolonged because of the necessity of a secondary operation for removal of bone grafts. If this case is excluded the average postoperative hospital stay of the remaining 14 was 10.2 days.

Since the operation in these cases in no way weakens the spine, early mobilization is encouraged. If sciatic pain persists in the immediately postoperative period and can be increased by jugular compression, the possibility of intradural nerve sleeve adhesions is considered. This condition is treated by increasing the spinal fluid pressure and thus distending the nerve root sleeve by placing a blood pressure cuff about the neck and inflating it to 40 millimeters of mercury for 5 minutes several times a day. As advocated by Gill and associates, we have also employed the following procedures: hydrocortisone in procaine is injected into the epidural space through the sacral hiatus, followed by passive or active straight-leg raising to mobilize the nerve roots and thus free them from possible remaining extradural adhesions.

SUMMARY

The pain in spondylolysis and spondylolisthesis is not due to displacement of or to movement between the bodies of the involved vertebrae. It is produced by the abnormal mobility of the unattached lamina. The surgical treatment should consist of removal of the unattached lamina together with the pathologic tissues surrounding the false joint. Spinal fusion is unnecessary: it prolongs convalescence and may serve to substitute one painful pseudoarthrosis for another.

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LYMPH FOLLICLES IN THE CERVIX UTERI

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LYMPH FOLLICLES are normal findings in many organs such as the small and large intestine (notably the vermiform appendix) and in those of the respiratory tract. These lymphatic follicles or nodules are either isolated or aggregated in smaller or larger groups and in various depths of the mucosa or submucosa. Less often they are found in the renal pelvis, ureters, urinary bladder, and urethra as well as in the conjunctiva, esophagus, and stomach. Lymph follicles in the mucosa of the entire urinary tract, as well as in the renal and prostatic parenchyma, are associated with a special form of inflammatory condition known as "follicularis."

One of us (N.J.D.) and other investigators have noted that true isolated lymph follicles can be found in or near the basal layer of the endometrium (not to be confused with the common focal aggregates of lymphocytes). They were found by Mönch in 18 per cent of the endometria of 227 uteri. Another of us (R.R.G.) had frequently observed true lymph follicles in the cervix, but it was surprising to find that little mention had been made in the literature about their presence in this particular part of the genital tract. Therefore, a study of the structure, frequency, and distribution of lymph follicles in the cervix uteri was undertaken. In order to determine whether these structures were congenital or developed later in life, fetal cervices were also studied.

The only "recent" mention of lymph follicles in the human cervix is in the textbook of *Histology* by Maximow and Bloom. This is information rather than mention since it consists of a drawing of the cervix containing a single lymph follicle beneath the squamocolumnar junction. No further information is given in the text about the frequency or structure of lymph follicles in the cervix. Moreover, that drawing (Fig. 511) was borrowed from Ebner, 1902, who also gave no further information in his text.

In 1908, Lesniowski reported a single lymph follicle in a cervical polyp and maintained that his was the first mention of lymph follicles in the cervix. He noted that the lymph nodule was associated with and surrounded by a "heavy round cell infiltration."

In a total hysterectomy specimen Hauser found a row of 6 lymph follicles in an area of "erosio simplex" in which the cervical mucosa was "filled with a round cell infiltration." This same area represented clinically a "mild ulceration." This author said that "whether these lymph follicles are the result of chronic inflammation or they are congenital structures, further investigation should show."

Mönch, in 1918 (p. 495) in his investigation of lymph follicles in the uterus cited before, mentioned in passing that he had found a single lymph follicle lying "within the heavily inflamed connective tissue of the cervix."

MATERIALS AND METHODS

The material on the adult consisted of slides from 29 cervices which had been serially blocked for another purpose. The number of sections examined from each cervix ranged from 10 to 80 with an average of about 30 sections per cervix. The sections had been stained routinely with the hematoxylin-eosin stain. The 12 fetal cervices were obtained in chronologic order from autopsy material. The fetuses were all well above 22 weeks of age, i.e., the age the lymph follicles are said to appear. Seven were still-

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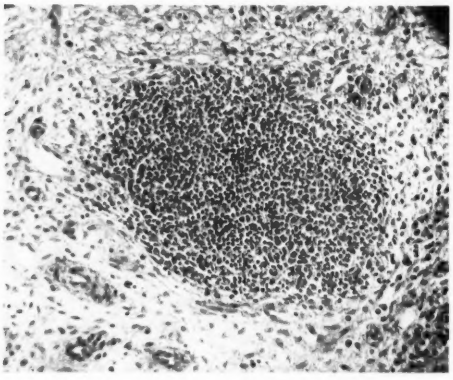

FIG. 1. A typical lymph follicle in the cervical stroma. × 140.

born while the remaining 5 were newborns who had lived for only a few hours after birth. An average of 20 sections were prepared from each fetal cervix, and these sections were stained with hematoxylin-eosin.

Also 86 multiple cervical biopsy specimens were examined, but often only a small part of underlying stroma was present, and thus many lymph follicles could easily have been missed.

MICROSCOPIC FINDINGS—GENERAL

Criteria were necessary for the differentiation of lymph follicles or nodules from dense or loose, diffuse lymphoid tissue. Detailed description is lacking in the literature of lymph follicles found in tissue other than in the lymph nodes themselves. The criteria adapted here were modified from descriptions of these structures in lymph nodes and are as follows:

1. A lymph nodule should be well circumscribed, round or oval, and may have circumferentially arranged connective tissue fibers, thus having a sort of pseudocapsule (Fig. 1).

2. It contains primitive reticular and reticuloendothelial cells plus more or less compactly arranged lymphocytes of any or all sizes, or a mixture of lymphocytes, lymphoblasts, and fixed histiocytes showing mitoses or phagocytoses (Fig. 2).

3. Usually there are one or more of the following: (a) blood vessels entering the hilum or leaving at the periphery of the follicle (Figs. 3 and 4); (b) small sized lymphatic vessel, afferent or efferent (Fig. 1); (c) cords or plates of lymphocytes and sinuses within the follicle itself or at the periphery; (The peripheral sinuses are similar to the lymph node sinuses but different from the occasional lymphatic vessel that surrounds a great part of a lymph follicle—Figs. 3 and 4); (d) a more or less thick periphery of closely packed small lymphocytes, i.e., a secondary follicle with germinal center.

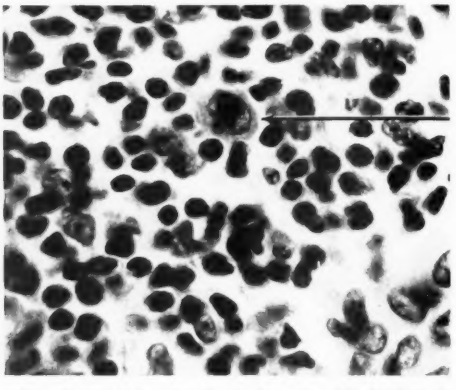

FIG. 2. A high power from the same follicle. Deeply staining lymphocytes and larger and lightly staining reticular cell nuclei are evident. The arrow points to a lymphoblast. × 640.

The lymph follicles were either directly beneath the cervical epithelium or deeper in the stroma of the cervix. These latter were usually not surrounded by any amount of inflammation and were either primary lymph follicles or secondary ones without germinal center.

Sometimes it was difficult to decide whether or not a given accumulation of lymphocytes or spotty chronic inflammation was a true follicle or just a "lymphoreticular island" as it is called by Furuta. In Figure 5 the lymphoid tissue, which is just under the endocervical squamocolumnar junction, is shown to be compact; there are mitoses as well as all sizes of lymphocytes,

fixed free histiocytes, primitive reticular cells, and lymphoblasts as well as blood vessels. This was called a "lymphoreticular island" and not a lymph follicle because it does not possess one of the major characteristics that a follicle should have, i.e., a circumscribed periphery; instead, the boundaries of this aggregate faded indistinctly into the neighboring parenchyma. This type of lymphoid tissue occurred immediately beneath the squamous or columnar epithelium, was associated with moderate or heavy chronic inflammation, and with one exception coexisted with lymph follicles. There were 5 cervices with these structures.

The lymphocytic infiltration or simple chronic inflammation surrounding a cervical gland or one of its branches sometimes was so thick and compact as to simulate a lymph follicle when cut tangentially. On closer examination, however, there was absence of sharp border, special blood supply, phagocytosis, or other special features that distinguish a lymph follicle or a lymphoreticular island from a simple lymphocytic infiltration.

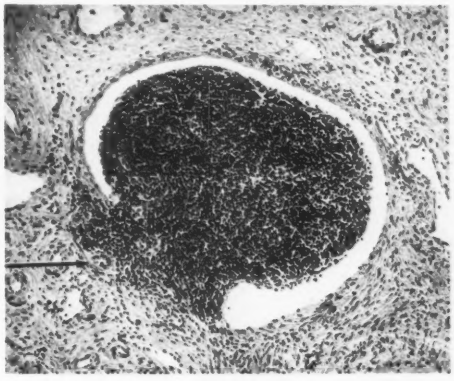

FIG. 3. A lymph follicle almost surrounded by a lymphatic vessel. The arrow points to a blood vessel entering the hilum. × 70.

THE LYMPH FOLLICLES IN THE ADULT CERVICES

Fourteen or 48.3 per cent of 29 serially blocked cervices contained lymph follicles. The number of follicles in a single section ranged from 1 to 8 with an average of 2.2 lymph follicles per section.

Another objective of this study was to determine the correlation, if any, between the presence of lymph follicles and the amount of inflammation in the cervical mucosa. Five or 35.7 per cent of the 14 cervices containing lymph follicles showed only a slight chronic inflammation. The rest or 64.3 per cent of the cervices with lymph follicles in the mucosa showed areas of moderate or heavy infiltration with chronic inflammatory cells although in 4 of the latter cervices some of the lymph follicles were found in areas showing slight chronic inflammation.

Three out of 15 or only 20 per cent of those cervices without lymph follicles contained heavy chronic inflammation and the rest or 80 per cent showed only slight spotty chronic inflammation. Two of those with heavy chronic inflammation showed acute inflammation, one slight and the other a true ulcer of the cervix. One of those with slight chronic inflammation had an area of infiltration with acute inflammatory cells. Incidentally, in one of these cervices without follicles but with heavy chronic inflammation, lymphoreticular islands were present.

In summary, 14 of 29 or 48.3 per cent of the serially blocked cervices contained

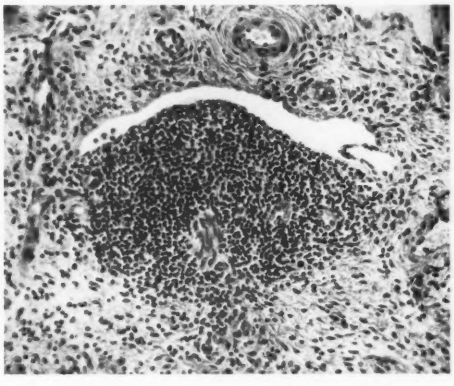

FIG. 4. A beginning or very small lymph follicle in the cervix. The cleftlike space is a lymphatic vessel. Blood vessels are entering the hilum. × 130.

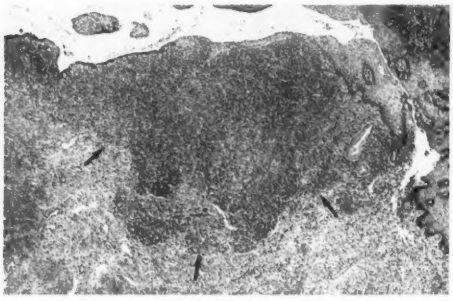

FIG. 5. The arrows outline a "lymphoreticular island" as described in the text. × 21.

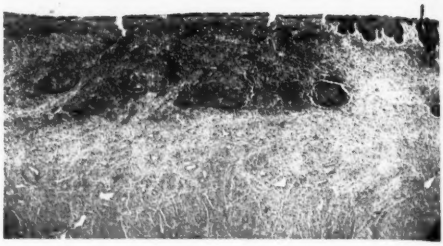

FIG. 6. Multiple lymph follicles. Five are present in this field from this markedly inflamed cervix. × 16.

lymph follicles. Heavy or moderate chronic inflammation was present in more than 3 times as many cervices with lymph follicles as without them. The reason for grouping the "moderate" and "heavy" group together and apart from the slight chronic inflammation is the well recognized fact that almost all cervices, whether associated with clinically manifested cervicitis or not, contain a slight amount of round cell infiltration.

It is interesting to note that of 86 multiple biopsy specimens examined, 8 contained lymph follicles and 6 or 75 per cent of those 8 were associated with marked chronic inflammation. Here, the incidence of lymph follicles is much lower than that in the serial blocked cervices, but this low incidence is easily explained by the fact that often in a biopsy only a small part of the stroma accompanies the epithelium and thus many lymph nodules could easily have been missed.

FETAL CERVICES

None of the 1 dozen serially blocked fetal cervices contained any lymph follicles in the cervix proper although all fetuses were at least of 26 weeks' gestation while the minimum age at which lymph follicles are found is 22 weeks. These fetuses had the capacity to form lymph follicles because with some of the cervices of the stillborn there was included in the sections either the appendix, or colon or a piece of omentum which showed definite primary lymph follicles. Moreover, 1 stillborn showed a typical primary lymph follicle in the adventitia of the cervix close to the vagina and a newborn showed a total of 5 lymph follicles in the adventitia of the vagina.

Incidentally, no inflammation at all was present in these fetal cervices. This latter observation is quite in contrast to the fact that in this study, as well as in the experience of every pathologist, the adult cervix is always associated with at least some lymphocytic and usually plasma cell infiltration—what is called here "slight chronic inflammation."

It has been shown that lymph follicles develop in a lymph gland as a result of the exciting influence of bacteria or their toxins. The appearance, therefore, of lymph follicles in the different kinds of mucosae may be associated with a bacterial invasion or similar toxic circumstances. The primary purpose of this article, though, was not to investigate the question of what causes the development of lymph follicles in the cervical mucosa, but rather to determine the frequency of occurrence and structure of the lymph follicles in the mucosa of the portio as well as their association, if any, with any marked and unusual amounts of inflammation. Although 2 previous reports in the literature dealt exclusively with the finding of 1 lymph follicle in one report, and 6 of them in a single cervix in another, the present studies indicated that 48.3 per cent of the 29

cervices examined contained lymph follicles. It also shows that there is a tendency for lymph follicles to be associated with moderate to marked chronic inflammation. Figure 6 is a typical picture of many lymph follicles in the middle of heavy chronic inflammation.

As has been stated, no lymph follicles were found in the mucosa of 12 serially sectioned fetal cervices examined. This observation supports the view that lymph follicles are not congenital structures, at least in the cervical mucosa, and that they appear to be associated with and probably are evoked or caused by inflammation.

It is universally accepted that a lymph follicle, in order to be called such, should be circumscribed. Nevertheless, associated with heavy chronic inflammation, we observed some special large lymphocytic aggregates (up to approximately 1½ to 2 mm. in their greatest diameter). Although their margins were not circumscribed and there was a gradual transition to the surrounding cervical connective tissue, these "lymphoreticular islands" showed most if not all the other characteristics of a true lymph follicle. In all cervices except 1 the lymphoreticular islands coexisted with lymph follicles and heavy or moderate chronic inflammation was present. Judging from the structure of these lymphoreticular islands and their similarity to the structure of a true lymph follicle, it seems likely that the function of these two structures is the same.

Finally, attempts were made to correlate the presence or absence of lymph follicles with (1) age and (2) gravity or parity of the patients. No correlation, though, could be found. Also no correlation could be found between the presence of lymph follicles in the cervix and the occurrence of either the secretory or proliferative phase in the endometrium at the time of the hysterectomy or surgical conizations of the cervix.

SUMMARY

1. The histology of the lymphoid tissue found in the cervix uteri is described. Special attention is given to the lymph follicles.

2. Of 29 serially blocked cervices from adults, 48.3 per cent contained lymph follicles. There was a positive correlation between the presence of lymph follicles in the cervical mucosa and the presence of moderate or heavy, chronic inflammation in the serially blocked cervices as well as in the 86 multiple biopsy specimens examined.

3. No inflammation and no lymph follicles were found in 12 serially blocked fetal cervices. Nevertheless, these fetuses were able at the time of their death to form lymph follicles in other tissues.

4. It was concluded that the lymph follicles in the cervical mucosa are not congenital structures but appear after birth and are usually associated with and probably result from chronic inflammation.

5. No correlation was found between lymph follicles in the cervix and age, parity, gravity of the patient, or menstrual phase of the endometrium.

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PREOPERATIVE MANAGEMENT OF BLOOD LOSS ANEMIA

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BECAUSE A BLEEDING LESION is often a surgical problem, patients who require surgery are often found to be anemic. Unfortunately, it is common practice to hospitalize these patients, build them up with transfusions, and then operate. While transfusion is required frequently when blood loss is acute and may be expected to continue at a rapid rate, transfusion therapy is rarely justified as the treatment for chronic blood loss anemia. The anemia of chronic blood loss is simply anemia due to a deficiency of iron, and safe, inexpensive, and convenient treatment with iron will invariably correct this condition. This article constitutes a brief review of the proper management of the iron-deficient presurgical patient.

Anemia due to chronic blood loss, iron deficiency anemia, is, when well developed, hypochromic and microcytic: the red cells are small and poorly filled with hemoglobin. In general, a history of chronic blood loss and the presence of hypochromic, microcytic anemia is sufficient evidence to establish the diagnosis of iron deficiency with a high degree of certainty. Thus, a red cell count, hemoglobin, and hematocrit as well as examination of the stained blood smear constitute all that is ordinarily required for diagnosis. In complicated cases, or when a history of blood loss cannot be elicited, staining the bone marrow for iron or determination of the plasma iron and iron binding capacity has been found to be very useful (1). The anemia of chronic blood loss is usually readily distinguished from that of acute blood loss by the history alone. Furthermore, hypochromia and microcytosis are absent when blood loss has been acute, and an elevated reticulocyte count will usually be present.

Because the anemia of chronic blood loss is simply due to iron deficiency, nothing else is needed to obtain an optimal response in its treatment. The addition of vitamin B_{12}, cobalt, copper, or any other substance is unnecessary and wasteful. Liver injections, unfortunately given frequently to patients with an anemia of chronic blood loss, have no effect whatsoever. The response of patients to adequate iron administration is dramatic. Oral therapy with inorganic ferrous salts is usually quite satisfactory. Occasionally, in urgent situations, especially when the reliability of the patient is in doubt, or in those situations in which there is an absorptive defect, as in sprue or after gastrectomy, intramuscular administration of iron-dextran may be advisable. The frequent use of this preparation, as shown in the case reports presented herein, was occasioned by a clinical evaluation at the time the patients were observed. Although parenteral therapy is frequently quite beneficial, its application in all of the cases presented should not be construed as an indication that parenteral therapy is always required.

Treatment of iron-deficient patients with blood transfusions is only rarely justified, and is usually contraindicated because of the considerable risk attendant to blood transfusion. Even under the best circumstances, the mortality rate accompanying blood transfusion is of the order of 1 per 1,000 to 5,000 transfusions. It is my belief that there are only three valid indications for transfusion in an iron-deficient patient:

1. Bleeding at a rate almost equal to, or in excess of, the capacity of the hematopoietic

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Under the auspices of the United States Atomic Energy Commission.

system to make red cells. It is important to recognize, however, the tendency to underestimate the capacity of the body to make blood when sufficient iron is available. Thus, Crosby's (5) patients who had hemolytic anemia could produce blood at 7 times the normal rate, and in his patient with hemochromatosis (6) and in our patients (2), there was no difficulty in maintaining a stable hemoglobin level when blood was withdrawn at the rate of 1,000 milliliters per week. Recent work in Block's laboratory indicates that normal subjects can probably replace blood at the rate of at least 1,000 milliliters per week when sufficient iron is supplied. It is surprising how little effect factors such as general health and nutrition usually appear to have on the response of iron deficiency anemia to iron, although the response may be limited somewhat by factors such as severe liver disease or chronic inflammation. Thus, in most anemic patients who are losing blood, even at a rate of 500 to 1,000 milliliters per week, it is quite reasonable to expect an increase in the hemoglobin concentration of their blood when adequate iron is supplied.

2. Situations in which the 3 to 5 week interval until the hemoglobin returns to levels satisfactory for surgery subjects the patient to danger greater than that of transfusions. For example, a severe recurrent hemorrhage that could be fatal may be expected to occur under some circumstances, or a malignant lesion may metastasize. In the majority of iron-deficient presurgical patients, however, the risk of waiting is small when compared with the risk of transfusion. This is particularly true in the case of women with menorrhagia of several years' duration.

3. Situations in which the anemia per se constitutes a risk to the patient. Such situations rarely if ever occur in the anemia of chronic blood loss. We have never seen such a case unless we consider those in which fear of increasing anemia due to renewed, severe hemorrhage is the chief consideration. If the patient was able to tolerate the anemia while ambulatory, it is difficult to believe

FIG. 1. Case 1. Response to iron therapy treatment.

that with some restriction of activity the patient cannot continue to tolerate the same degree of anemia while undergoing treatment. The amazing capacity of individuals with low hemoglobin levels to get about adequately is well known and is illustrated in Case 1.

The following case reports are presented to illustrate certain of these considerations in the management of presurgical iron-deficient patients. Each patient was seen at the University of Chicago Clinics.

CASE REPORTS

CASE 1. A 41 year old Negro female presented herself at the outpatient clinic complaining of feeling weak and tired, and of being unable to get enough sleep. She dated her complaints to her previous menstrual period during which bleeding had been quite severe, but admitted some increasing listlessness for approximately 6 months. One month prior to admission, she had seen a physician who said that she was anemic and treated her with a "shot" and some vitamin capsules. She had continued to work as a domestic servant until her visit to the University of Chicago Clinics. The diagnosis was severe anemia and the patient was hospitalized. On physical examination, the uterus was enlarged and irregular. Blood counts showed the hemoglobin to be 3.3 grams per cent, red count 1.86 million, and the hematocrit 12 per cent. Hypochromasia of the red cells was very marked in the smear. A few nucleated red cells were seen. No blood transfusions were given. Ferrous sulfate was administered orally and iron dextran, intramuscularly. Her response to this treatment is illustrated

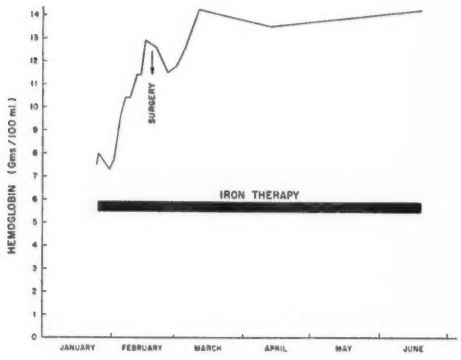

FIG. 2. Case 2. Response to iron therapy treatment.

in Figure 1. As indicated, the hemoglobin returned to 13.4 grams 8 weeks after the institution of therapy in spite of 2 moderately heavy menstrual periods in the interim. She was then rehospitalized, and a hysterectomy was performed. No blood transfusions were necessary.

Although iron deficiency anemia was quite severe in this instance, it is evident that a patient able to perform the work of a domestic servant with a hemoglobin level of 3.3 grams per cent should experience no difficulty in tolerating restricted activity at the same hemoglobin level. The uterine disease was undoubtedly of long standing and was benign. It was obvious from the marked degree of hypochromia that the anemia was due to iron deficiency and not to acute blood loss. Bleeding, although relatively heavy, was intermittent, and there was no reason to suppose that it exceeded the regenerative capacity of the marrow. She responded dramatically to iron therapy, as such patients invariably do, and was spared the danger of blood transfusion.

CASE 2. A 60 year old white housewife had consulted a physician 5 months previously because of fatigue. She was found to be anemic, and vitamin B_{12} was given intramuscularly, at first twice, and then 3 times, a week. Liver injections were also given. When the anemia failed to respond to treatment, blood transfusions were administered on 2 occasions. The past history revealed that 1 year previously 3 polyps had been removed from the sigmoid colon proctoscopically. Physical examination was not contributory. Upon hospitalization the hemoglobin was 8.0 grams per cent, red count 3.45 million, and hematocrit 29 per cent. Some hypochromia of the red cells was present in the blood smear. Stools gave up to 3+ reactions for blood with benzidine. Iron therapy was instituted in the form of intramuscular iron dextran. Response to treatment is shown in Figure 2. Results of a complete gastrointestinal roentgenographic series and proctoscopic examination were negative. A tube was passed along the gastrointestinal tract and benzidine positive material could be aspirated when its tip reached the level of the transverse colon. An exploratory laparotomy was carried out, but the bleeding point could not be located. Since surgery the patient has been managed successfully with orally administered iron sulfate.

This patient's history emphasizes the importance of an accurate diagnosis of anemia. It demonstrates the futility of treating such patients with vitamin B_{12} or liver. It is evident that if proper iron therapy had been instituted at an earlier date the 2 blood transfusions could have been avoided. Fortunately, in this case, the transfusions were not followed by any serious complications, but this is by no means always true. In this case, iron therapy was administered while appropriate diagnostic studies were being made, and the response was almost complete by the time surgery was undertaken.

CASE 3. A 62 year old white housewife was seen in the outpatient department with a complaint of anemia of 2 years' duration. She had been hospitalized elsewhere during this period and had received 2 blood transfusions on each of 4 occasions. In addition, liver and vitamin B_{12} injections had been given weekly as well as 1 liver and vitamin B_{12} capsule daily. She was given iron occasionally. A record of blood counts taken during this period clearly indicated the presence of a hypochromic anemia. Results of roentgenographic examination of the gastrointestinal tract 2 years previously, at the onset of illness, were negative. However, several months before being seen here, roentgenography of the colon revealed a filling defect, but operation was refused. Physical examination now revealed a mass at the right side of the abdomen which was present intermittently. On admission to the hospital, the hemoglobin was 9.9 grams, red count 3.82 million, and hematocrit 33 per cent. Slight hypochromasia of the red cells was present in the smear. Three stools all gave a 4+ reaction for blood with benzidine. While roentgenographic examinations were being carried out, iron deficiency anemia was being treated intravenously with saccharated iron oxide. Roentgenograms revealed no lesion of the gastrointes-

tinal tract, but after some reluctance, the patient was persuaded to undergo exploratory laparotomy. At surgery, 25 days after the institution of iron therapy, the hemoglobin was 11.8 grams per cent. A carcinoma of the ascending colon was found to be penetrating the serosa. An uneventful hemicolectomy was performed. No blood transfusions were necessary. Eight months later, an inoperable recurrence was found.

Unlike Case 2, the iron deficiency in this patient was due to bleeding from a malignant lesion. In this case, the 8 transfusions not only represented an unnecessary risk to the patient whose anemia could well have been treated with iron alone, but also served as a substitute for an accurate diagnosis. Postmenopausal iron deficiency anemia almost always is due to gastrointestinal bleeding. Earlier awareness of the gastrointestinal bleeding might have led to eradication of this now inoperable carcinoma.

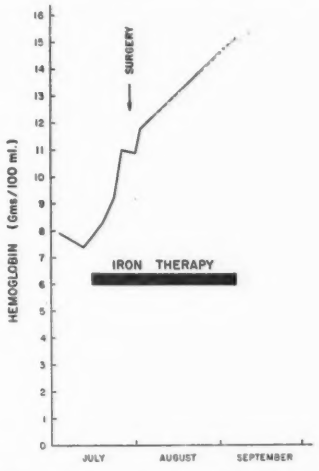

FIG. 3. Case 4. Response to iron therapy treatment.

CASE 4. A 49 year old white housewife was admitted to the hospital because of extreme nervousness and sleeplessness of 4 months' duration. She had suffered from bleeding hemorrhoids for many years. There had been episodes of fairly profuse bleeding for the past 18 months. For the past 10 years, she had been taking iron intermittently for mild anemia. She used alcohol excessively. On physical examination, the liver was found to be palpable 4 centimeters below the costal margin and the spleen was palpable 2 centimeters below the left costal margin. The results of laboratory examination revealed liver function tests to be normal. The hemoglobin was 7.4 grams per cent with a red count of 2.73 million and a hematocrit of 26 per cent. The smear indicated the presence of a moderate degree of hypochromasia, anisocytosis, and poikilocytosis. In spite of normal red cell indices, treatment with ferrous sulfate orally and iron dextran intramuscularly was instituted because of the clear-cut clinical history and the typical appearance of the red cells in the smear. Blood counts taken 3 days later showed hemoglobin to be 7.9, red count of 3.5 million, and hematocrit of 30 per cent. Marked symptomatic improvement was noted, and the hemoglobin rose rapidly as indicated in Figure 3. Hemorrhoidectomy was carried out uneventfully.

CASE 5. A 30 year old Negro female was admitted to the hospital because of the increased size of the abdomen and recurrent metrorrhagia. Upon physical examination, the uterine corpus was enlarged, nodular, and irregular. Hemoglobin was 5.6 grams per cent, red count 3.77 million, and hematocrit 25 per cent. The red cells were found to be markedly hypochromic and microcytic on smear. The electrocardiogram was negative and serology was positive. The patient was given 2 units of blood following which she suffered a mild pyrogenic reaction. No iron therapy was given. The following day a complete hysterectomy and bilateral salpingo-oophorectomy was carried out under cyclopropane and oxygen anesthesia. Five hundred milliliters of blood were given during surgery. At the conclusion of surgery, pulse and respiration were normal. A few minutes later, the patient's feet were noted to be cold and the pulse was absent. In spite of intracardiac coramine and oxygen therapy, the patient could not be revived. The findings at autopsy were compatible with the clinical impression of postoperative cardiac arrest.

It is, of course, impossible to determine whether the iron deficiency and the occurrence of cardiac arrest postoperatively were related causally. The case is presented, however, because it illustrates another, at least theoretically valid reason for the treatment of iron deficiency anemia with iron. Ott has suggested that iron deficient subjects may be particularly prone to postoperative circulatory failure. Although his clinical and experimental evidence are not convincing, the theoretic basis for this belief may well be sound. The iron-deficient individual should be regarded as a person with a deficiency state that affects not only the blood but also the tissues. Although it was formerly believed that the tissue iron enzymes were not

affected by iron deficiency, recent experimental observations by Gubler and associates and Beutler (3) have indicated that a profound depression in tissue enzymes may indeed take place in iron-deficient animals. Although transfused whole blood contains large amounts of iron, this iron is firmly chelated in the hemoglobin molecule and is not immediately available to supply the tissue needs for iron.

More work is required to delineate clearly the risk of operating upon iron-deficient individuals, but until such evidence is available, it is advisable to treat iron deficiency with iron in a readily utilized form even if blood transfusions are necessary to restore the hemoglobin level.

SUMMARY AND CONCLUSIONS

The anemia of chronic blood loss is due to a deficiency of iron. It is diagnosed with ease in most instances. Liver, vitamin B_{12}, folic acid, and other vitamins are of no known value. Transfusions are justified only if: (1) the rate of bleeding is very rapid, (2) immediate surgical intervention is important, or (3) the anemia per se subjects the patient to a real risk exceeding that of transfusion. Five cases illustrating these precepts are presented. With the exception of Case 5, the cases presented are not unusual. The idea that iron, not blood transfusions, is the treatment of choice for the anemia of chronic blood loss is not new. Yet, it is apparent that the basic precept that iron deficiency should be treated with iron is sometimes forgotten by many physicians.

It is to be hoped that greater awareness of the importance of accurate diagnosis of anemia and of the dangers of blood transfusion, will cause transfusion of patients with chronic blood loss to become a relatively rare event in the foreseeable future.

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EDITORIALS

SPECIALIZATION VERSUS GENERALIZATION, THE DILEMMA OF SURGICAL TRAINING

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TWENTY YEARS AGO, when the American Board of Surgery was founded, it stimulated young surgeons to obtain better training in general surgery and raised the standards of surgical practice. At that time, the surgical specialties were not well developed. In most general hospitals and in some university hospitals, the work in many of the now special fields was done by general surgeons. Twenty years ago, therefore, general surgery was indeed general surgery, and the influence of a general surgical board was constructive in promoting better practice.

Today not only have orthopedics and gynecology developed their own specialty boards, but in these services most large hospitals have developed their own departments. In addition, the specialties of thoracic surgery, plastic surgery, and proctology (including colon surgery) have come of age, developed their own boards and their own services. The specialty of vascular surgery promises to follow a similar course. What then remains in general surgery? In a hospital in which the specialty services are mature, the thyroid, the breast, the upper abdomen, and hernias are all that is left on a general surgical service.

In a hospital with strong specialty services, each service has its own training program and its own senior residents. General surgical residents may rotate through the surgical specialties, but on these services it is not the general surgical residents but the specialty residents who have the senior positions and do the operations. In such a hospital, the operative experience of the general surgical resident consists of doing the surgery of the thyroid, breast, upper abdomen, and hernias. Yet these same young surgeons, if they go into practice in small communities, will be called upon to do mainly gynecology, operations for the treatment of trauma, and a wide variety of operations in every subspecialty field.

The obvious answer to the problem of training the general surgeon in trauma, fractures, gynecology, and the various specialties is to maintain a dominant general surgical division in which operations of all kinds are done. But general surgery cannot monopolize the teaching material of the surgical specialties without impeding the development of the specialties. The relationship of general surgery to the surgical specialties is like that of a father to his sons. When children are mature and independent, too much control by the parent may be detrimental to their development. After maturity it is not control that is needed but co-ordination of independent units.

The policies of the American Board of Surgery have a great influence on training programs and therefore on the organization of hospital services. If the Board insists that its applicants be trained to perform a wide

variety of operations in fields that overlap the fields of the surgical specialties, it will exert a strong influence toward perpetuating the dominance of general surgery at the expense of the surgical specialties. This will lead to the development of a "general practice" type of surgeon and will impede development of special skills that come with concentrations of effort in narrower fields.

An alternative would be to give, at the end of the second or third year, an examination that covers the theoretic aspects of general surgery and all the surgical specialties. This would be a measure of basic training and a prerequisite for training in any surgical specialty. Following this procedure, if the surgeon wished to specialize in the surgery of trauma, in abdominal surgery, in vascular surgery, or in any of the existing surgical specialties, he could take specialized training, obtain operating experience in the field or fields of his choice, and then be examined in the specialties he chooses to practice.

The development of the specialties is forcing general surgeons to choose whether they wish to maintain dominant general surgical departments without much specialization or whether they wish to encourage superspecialization. Perhaps, before there is nothing left to specialize in, general surgeons should define general surgery and make a specialty of what remains in that field.

BEHOLD, THE TORCH!

R. MORTON BOLMAN, M.D., F.A.C.S., Fort Wayne, Indiana

To you from failing hands, we throw the torch—
Be it yours to hold it high!
If ye break faith with us who die
We shall not sleep, though poppies grow
In Flanders fields.
Captain John D. McCrae—1918

THOSE who do not heed the mistakes of the past must expect to repeat them. This truism can as well be applied to surgery as to any form of endeavor—political, educational, scientific, or industrial. In times gone by a surgeon was a man bolder than most, who pushed against the mortal limitations of his time with varied and changing results. He was incapable of being judged because he was so in the minority, and who was to judge. He might build a great name on a basis of personal charm and magnetism when actually these attributes far outshone his real worth. Again, by sheer skill and deftness, he might convert night into day, but only his own superior talent could do this, and his advances were not far-reaching. Realizing the limitations of his armamentarium, he was more than apt to be humble, kind, and sympathetic, though each of us can remember his bombastic counterpart. He became an artist in the deliverance of news that was frequently somewhat less than encouraging. He learned to present a defeat to a family in terms that made it seem God's will. To the humble and the down-trodden he became, in fact, God's own representative, more so even than the clergy. When failure was inevitable, the family adopted an attitude of "so be it; The Great Man has said so." This was the hold of the profession on a trusting public. Inevitably men came along who recognized the financial possibilities of this childish and religious faith. They wore the same clothes, mouthed the same words, and put on the same expressions as their giant predecessors, but the product they delivered was a rank imitation of the humble service of a great surgeon. Unfortunately, these people seem to seek each other so that the surgeon found his nefarious medical counterpart. The one sought out the prospect, and the other closed the deal. Both went away somewhat richer and the only one who lost was the patient.

Since these two surgeons looked so alike, sounded so similar, and acted so much the same, the patients became confused in their search for the true surgical doctor. Frequently, the wrong choice was made, and each time this occurred, a new group of people became suspicious of all medicine in general, and lost our gem of great price, their boundless faith.

All change is so gradual that alarm spreads slowly, and by the time the thinkers in our midst began to hear of this defection, much harm had already been done.

In an honest attempt to help re-establish the faith of the public, as well as to elevate the sights of all of us, the American Boards and the American College of Surgeons began to standardize certain minimum requirements—the one for training, the other for moral fitness. These were resisted unto death by groups which usually had at their center a man whose very existence depended on the *status quo*. Any change for the better would necessitate that he should improve or expire. In all fairness, some resistance came also from those who sensed change and instinctively feared it.

We were told that we must not air any of our problems. The public must not know; we must police our own ranks quietly. We were given our chance to do this, but who among us welcomed the task?

There are now trained men to judge trained men, societies to assure against improper inducement for profit, and organiza-

tions whose sole aim is to re-establish the surgeon in the same high esteem that used to be his for the asking.

We now have the training means, the research, the technique, and the know-how, but where is the humility and the great heart that made our forefathers so close to their patients, so much a vital part of the community? To look down on the most humble patient is a confession of ignorance. He brings you his temple, created in the image of God, and gives to you the enviable privilege of attempting to refashion it in a more physiologic manner. This is the torch thrown to us from those great men of the past, whose knowledge was so infinitesimal, but whose hearts and whose humility reached to infinity. The combination of the training and ability of today wed inseparably to the humility, sympathy, and sense of privilege of yesteryear would produce a generation of surgeons who in one lifetime could replace surgery on the pedestal which it so justly deserves.

"Be it ours, then, to hold it high," and to realize that our concern is to learn from the past; to add to it with the present so as to assure a position of integrity, trust, and acceptance for surgeons of the future—Behold, the torch!

THE SURGEON AT WORK

THE TECHNIQUE OF ANASTOMOSING SMALL ARTERIES

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THE BASIC TECHNIQUE for arterial anastomosis utilizing the simple method of circular suture was developed in the first decade of this century by Carrel and Guthrie. The clinical application of blood vessel anastomoses on a large scale, however, was not achieved until 1945 when Crafoord and Gross reported the successful treatment of cases of coarctation of the aorta by resection with end-to-end anastomosis. These reports stimulated a revival of interest in the early work of blood vessel suturing, resulting in the employment of direct excision and replacement of aneurysms and occlusions of the major arteries. The success achieved with these techniques in large vessels is noteworthy at this time and, in part, is related to the advances in the ancillary aspects of surgery, such as anesthesia, blood transfusion, and antibiotics.

Interest is now focused on problems involving small vessels, such as the coronary arteries. A dependable technique for the performance of successful small arterial anastomoses has numerous clinical applications. Among these are the repair of acute operative injury to vital arteries such as the hepatic or renal, the excision of aneurysms of these vessels, or the restoration of an adequate blood supply to jeopardized organs because of neoplastic, thrombotic, or embolic occlusion of their visceral artery. An experimental program has been in progress since 1950, involving anastomoses of arteries varying in diameter from 1½ to 4 millimeters. In this communication the fundamental principles and operative details of successful small arterial anastomoses are presented as they have been developed in this laboratory.

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METHOD

Mongrel dogs were used, weighing from 25 to 75 pounds. All operations were performed under general anesthesia produced by a veterinarian solution of nembutal administered intravenously. The small arteries that were used for anastomoses in various experimental studies were the renals, splenic, superior and inferior mesenteric, hepatic, superior thyroid, peripheral branches of the superior mesenteric, internal mammary, coronary, and intracranial vessels (6-12). To date our experience includes more than 300 small arterial anastomoses.

The basic technique used in most of the anastomoses was a continuous over-and-over suture. Obliterative thrombosis at the suture line is the most common cause of failure and only by refined meticulous technique can this complication be avoided.

FUNDAMENTAL PRINCIPLES OF ANASTOMOSING SMALL ARTERIES

The vessels must be handled gently at all times. Special care should be exercised to avoid pinching the transected end of the vessel with a forceps. Injury to the intima will invariably cause thrombosis in small arteries.

The terminal 3 millimeters of the vessels must be stripped completely of adventitia. Should strands of adventitia fall into the suture line or be carried into the lumen by the sutures, thrombosis is a certainty.

Fine bull dog clamps whose springs have been

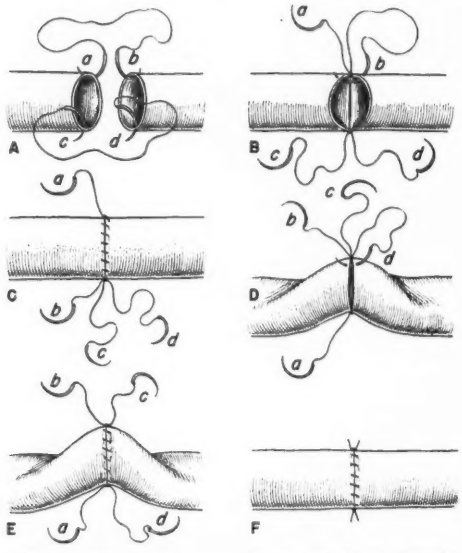

FIG. 1. Continuous over-and-over technique of small arterial anastomosis. See text for detailed description.

weakened by forcible compression are used. Failures have resulted from thrombosis at the site of vessel injury due to the temporary occluding clamp.

The transected ends of the vessels should be irrigated frequently with isotonic saline to prevent drying and to wash away all blood and clot from the lumen. A 20 cubic centimeter syringe and a fine blunt edged needle are used.

Smooth approximation of the intimal surfaces without constriction prevents the production of abnormal eddies resulting in vegetations and thrombosis. The incidence of failure is higher when there is a discrepancy in vessel size greater than 2 millimeters.

Twelve inch lengths of No. 7-0 braided silk, armed at each end with an .008 inch wire 3/8 circle, taper point, round atraumatic needle are used. The suture is lubricated by passing it through the subcutaneous fat of the animal. The fine needle and suture produce a minimum of trauma or reaction. There also is no bleeding from the needle puncture sites, since the aftercoming No. 7-0 silk is slightly larger in diameter than the needle and it plugs the opening.

Removal of the temporary occluding clamps almost always results in some bleeding from the suture line. Gentle nonocclusive pressure with a small dry gauze pad for 5 to 10 minutes will control most leaks by allowing them to seal spontaneously by fibrin deposition. Extra sutures may produce irregularity in the suture line and subsequent thrombosis.

Aseptic technique is essential for successful arterial anastomosis.

OPERATIVE DETAIL

Continuous over-and-over suture. After the vessels to be sutured are exposed and temporarily occluded, they are cut smoothly with small sharp scissors. The excess blood is washed out by irrigating with saline, and a final attempt is made to remove every last strand of adventitia near the edges. The ends of the two vessels are aligned by 2 sutures placed at the lateral angles and tied without tension (Fig. 1A). The use of suture material with a needle at each end makes it possible to pass the needle from the intimal surface of each vessel to the outside. This is one of the essential features of the technique being presented since it eliminates the hazard of catching a fine fragment of the opposite wall and destroying the patency of the anastomosis. An assistant supports one end of the far angle suture in one hand and both ends of the near angle suture in the other hand, exerting a minimum of tension on the vessels. The other end of the far angle suture is used to unite the anterior walls of the vessels by a continuous over-and-over stitch (Fig. 1B) and is tied without tension to one end of the near angle suture (Fig. 1C). Visualization of the posterior walls is achieved by rotating the vessels on their long axis. This is done by passing the remaining single end of the far angle suture posterior to the vessels, while the three ends of the near angle suture are passed anteriorly (Fig. 1D). The posterior suture line is accomplished with one of the three far ends (Fig. 1D). This is tied, finally, to the one near angle suture (Fig. 1E, F).

There are several aspects of the operative technique that require special consideration:

The operator and the assistant who holds the angle sutures must eliminate all extraneous movement by stabilizing their hands on an immobile portion of the operative field. This precaution enhances accurate and atraumatic passage of the needle through the vessels.

The complete passage of the needle through the vessels should be performed by the operator only. Since the operator is in the proper position and balance, excess movement and enlargement

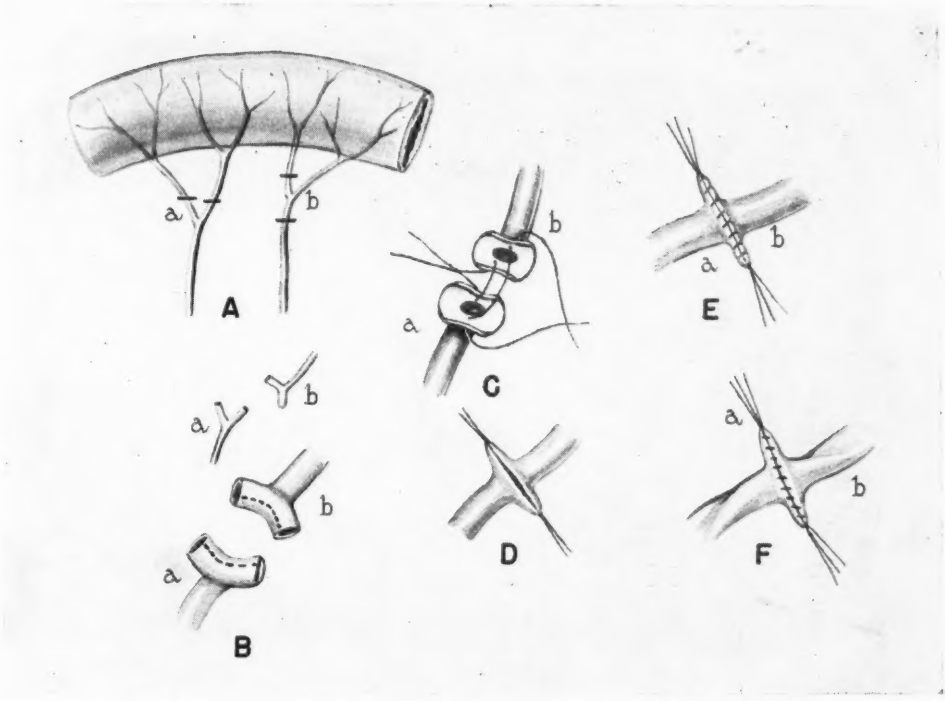

FIG. 2. Flange method of small arterial anastomosis. See text for detailed description.

of the needle puncture site through which bleeding can occur are avoided.

The stitch includes all layers of the vessel wall and all bites of the needle are meticulously placed less than 1 millimeter from the cut end of the artery and less than 1 millimeter apart. The first and last stitches in each row must be placed extremely close to the angle sutures in order to avoid annoying bleeding from the angles.

The flange method of small arterial anastomosis. This method permits small arteries to be anastomosed without narrowing the vessel lumen and without the sutures ever being exposed to the lumen. The flange method is limited in that the two vessels to be joined must have a branch which may be sacrificed safely.

The two vessels to be anastomosed are cut at a bifurcation (Fig. 2A).

The "Y" or "T" thus formed is slit along the center of the free border of the horizontal limb (Fig. 2B), producing a vessel with a flange of tissue surrounding the lumen. The flange is trimmed down to a circular rim measuring 1½ millimeters.

The flanges are approximated with 2 No. 7-0 braided silk atraumatic arterial sutures placed opposite each other in the crotch of the previous bifurcation (Fig. 2C and D).

A continuous over-and-over stitch is placed along the anterior border with one end of the far angle suture and tied to one end of the near angle suture (Fig. 2E). The vessel is then rotated and the posterior border is similarly sutured (Fig. 2F).

Each stitch must be taken at the edge of the lumen incorporating the entire flange in the suture line. A potential space for aneurysm or clot formation is thus avoided.

DISCUSSION

It has been the experience of most investigators in the field of arterial suture, that the percentage of successful results decreased markedly when one was working with vessels of extremely small size.

However, as experience with small arterial anastomoses accumulated in this laboratory, success with vessels of 1½ to 4 millimeters became the rule rather than the exception. Failure was usually due to some violation of the fundamental principles and operative detail as presented in the foregoing. Anticoagulants were not necessary for success and certainly are no substitute for meticulous technique.

Although an everting type of suture might seem preferable in most vascular surgery, according to Shumacker and Lowenberg, the degree of narrowing of the vessel lumen produced by such a method makes its use unsatisfactory in arteries of this small caliber. In a study by Holman and Hahn, a series of vessels approximated by interrupted everting mattress sutures and by the continuous over-and-over suture demonstrated an average decrease in cross-sectional area of 15 and 8 per cent, respectively.

There have been 3 successful clinical applications of small arterial anastomoses at this clinic in the past 2 years. A left splenorenal arterial anastomosis was constructed in a 44 year old man with ascending thrombosis of the aorta extending to just below the origin of the renal arteries (9). A luetic aneurysm of the thoracoabdominal aorta involving the celiac and superior mesenteric arteries was resected and replaced by an aortic homograft. The visceral arteries were anastomosed to the corresponding branches of the homograft (8). Immediate reconstruction of the cervical esophagus was performed in a patient who had a resection for carcinoma by revascularizing a free segment of jejunum in the neck. An end-to-end arterial anastomosis was performed between the radial branch of the superior mesenteric artery and the inferior thyroid artery, both measuring 2½ millimeters in diameter (12). The technical details of the small venous anastomosis will be included in the report of this procedure.

SUMMARY

1. The fundamental principles and operative detail of successful small arterial anastomoses are presented.

2. The clinical application of small artery anastomoses is discussed in relation to injury, aneurysm, or thromboembolic occlusion of essential vessels, as well as to organ replacement.

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TELEVISION RADIOSCOPY DURING OPERATIONS ON THE BILIARY PASSAGES

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In 1952 I described the technique of manometric and roentgenographic examination of the biliary passages during operation (1), and gave the conclusions I had reached after an experience of 10 years and 1,500 cases. At the present time, the number of operations performed in this way has risen to 3,000; and for the last year I have been using television radioscopy in addition to the methods already described. Everyone who has used radioscopy in the examination of patients with biliary drainage knows how much the method facilitates physiopathologic interpretation and the reading of cholangiograms. However, hitherto radioscopy has not been available to the surgeon in the operating room, where, in order to reduce the number of radiographs required, he has used manometry of the biliary passages to assist in the interpretation of the x-ray films.

Various devices have been suggested to secure radioscopic control during operation, for example, Porcher had an assistant lying in a "coffin" placed under the operating table. But this procedure gives the radiologist the decisive opinion in the choice of procedure, and the surgeon becomes a mere technician without any say in the selection of operation, an unacceptable position, because the surgeon must retain both moral and legal responsibility for the operation.

The electronic lens (image amplifier) used in cineradiography provides a method by which the radioscopic image can be seen in daylight through a viewer which restores the image to its correct size without reducing its clarity; but this picture is available only to the person using the viewer, which the surgeon finds difficult to do because of the need to preserve asepsis.

Television radiography solves this difficulty because the image can be seen by the surgeon and his assistants, and can be relayed throughout a whole operating suite.

The apparatus includes: (1) a portable x-ray set, working at 70 kilovolts and 1 or 2 milliamperes; (2) an image intensifier with a circular field 12.5 centimeters in diameter; (3) an optical device to transmit as bright and clear an image as possible; (4) a small television camera, of very high sensitivity since the images are not so bright as those usually televised; (5) a control stand containing the camera mechanism, the amplifying apparatus, current stabilizers, the regulating panel for the various adjustments and the screen for the operating room; (6) additional television receivers relayed from the control stand through coaxial cables; (7) a cinecamera synchronized with and focussed on one of the receivers. The specifications for the television are those usual in France: 819 lines, 25 images per second, and horizontal definition better than 700 bars.

The tube is placed below the operating table (which is not radio-opaque). The composite image amplifier-television camera (68 cm. high) is fixed to the upright of the portable apparatus, brought over the patient, and centered over the tube.

Although not used as a routine in the surgery of the biliary passages, in the last year television radioscopy has been employed 200 times. It does not replace either radiography or manometry; rather it adds to the usefulness of both. It is possible to make use of radioscopy in the intervals between the development of films without disturbing the arrangements for preoperative manometric and radiographic control. But most information is obtained if radioscopy is done immediately after readings of pressure have been made. From the first the drop-by-drop injection of the contrast medium is followed on the screen. Often agreement between manometric and radioscopic data completes the diagnosis at once and it is sufficient to take one control radiograph for record purposes. The total time occupied by the investigations can then be halved and does not exceed 5 minutes.

Radioscopy can provide new precision in the investigation of cases of stone in the common

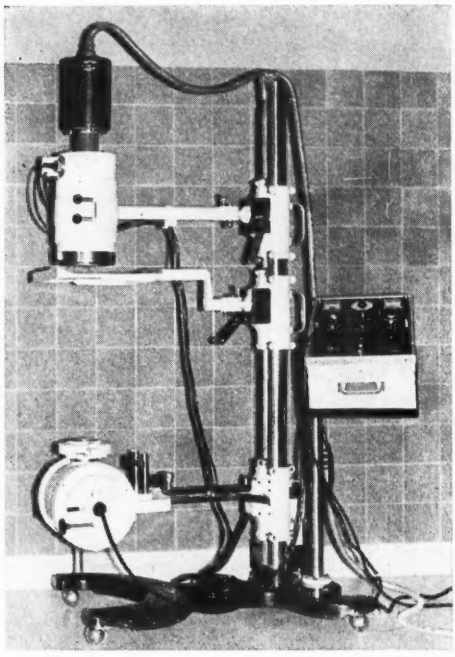

FIG. 1. The portable x-ray set combined with an image intensifier and above it the television camera.

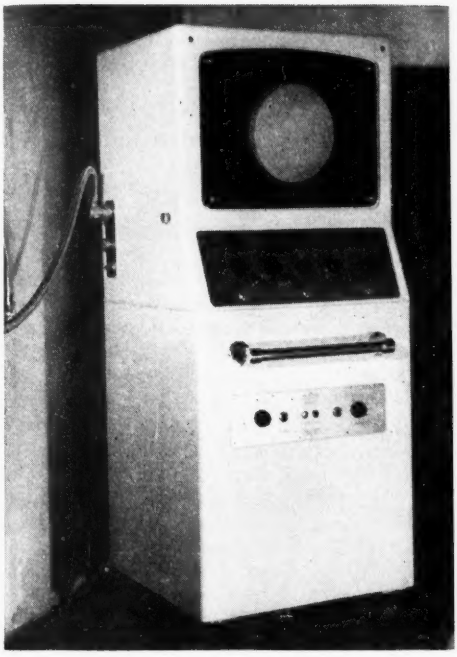

FIG. 2. The screen with the regulating panel for the various adjustments.

bile duct: (1) In detecting small nonobstructing stones. After the first few drops of medium have been injected, a transitory dark thin streak appears between them. (2) To exclude a diagnosis of stone based on a filling defect. Radioscopy shows this to be an artefact arising from the incomplete superposition of the outline of the common bile duct and the duct of Wirsung. (3) Especially when a succession of control radiographs would otherwise be necessary in the course of clearing an obstructed common duct, a glance at the screen will tell at once if the obstruction has been removed.

Radioscopy can help in the early diagnosis of growths of the ampulla of Vater, before the onset of jaundice, by outlining irregularities of the papilla or by demonstrating a transient narrowing or a transient dilatation, after which the outline returns to normal.

In the realm of physiopathology, analysis of dystonia of the sphincter of Oddi is very easy on the radioscopic screen.

Finally, it is the surgeon in the operating room who himself has at his disposal all these complementary pieces of evidence; it is the surgeon himself who without any loss of time draws his own personal conclusions from them.

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A TECHNIQUE FOR THE TEMPORARY CONTROL OF BLEEDING DURING TRANSESOPHAGEAL SUTURE LIGATION OF ESOPHAGEAL VARICES

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TRANSTHORACIC SUTURE LIGATION of bleeding esophageal varices is now an accepted procedure. This technique was first described by Boerema in 1949 but has attained popularity through the efforts of Crile, Linton (3, 4), and Linton and Warren (5).

The indications for this operation vary from clinic to clinic, some preferring it as a desperate measure to be used only when more conservative management has failed. Others regard it as the procedure of choice for most patients who are bleeding massively from esophageal varices. Linton has shown that valuable time may thus be gained in patients with cirrhosis, during which their condition may be improved prior to a definitive shunting procedure.

Every surgeon who has had occasion to perform this operation has been impressed with the rather alarming blood loss which accompanies an incision through the wall of an esophagus containing large distended varices. Vision is obscured, prolonging the procedure and making it technically more difficult. The additional blood loss may be critical in a patient who has bled massively and who is bordering on or may be in overt shock. Therefore, the production of a bloodless field would serve two purposes: (1) to prevent further blood loss and (2) to make it possible to carry out the operation more accurately and with dispatch, since operating time may also be vital in such a patient.

I have utilized the described technique in 3 patients with highly satisfactory results.

TECHNIQUE

A Sengstaken tube may be left in place while the thoracotomy incision is being made. As soon as the pleural space is opened, the mediastinal pleura is incised longitudinally for 4 to 5 inches beginning just superior to the esophageal hiatus. Then the esophagus is rapidly mobilized at a point 1 to 2 centimeters above the diaphragm by using finger dissection. A ¼ inch umbilical tape is placed around the esophagus at this point and incorporated into a Rommel tourniquet. The intraluminal balloon is deflated and removed. Moderate constricting pressure is then exerted, which will occlude the varices. This maneuver requires less than 1 minute.

With the tourniquet in place, a 10 to 15 centimeter longitudinal incision is made through the wall of the esophagus. The varices are then oversewn after the technique of Linton. It will be observed that the operative field is practically bloodless, yet the varices will usually remain distended and easily seen. If hemostasis is not complete or if the varices empty and become invisible, a second tourniquet may be applied just below the aortic arch (Fig. 1).

After completion of the procedure the tourniquet may be released and the stomach emptied

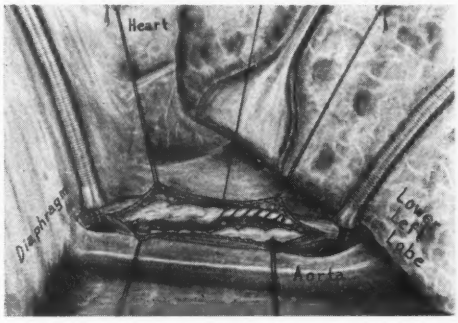

FIG. 1. Drawing demonstrating the use of 2 tourniquets to occlude esophageal varices after which a longitudinal incision is made into the lumen of the esophagus and the varices are oversewn with a continuous catgut suture.

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The opinions or assertions contained herein are the private ones of the author and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

of the rather large amount of blood usually present. The cardiac area is then inspected and, if necessary, the incision may be extended into the stomach if additional varices are found which require further suturing.

SUMMARY

A simple modification of technique for the control of bleeding from the esophagus during transthoracic suture ligation of esophageal varices is presented. It is a safe and quickly applicable method. It facilitates the operation and reduces blood loss.

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A TECHNIQUE EMPLOYING HYPOTHERMIA FOR THE REPAIR OF ATRIAL SEPTAL DEFECTS

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AFTER FIVE AND ONE-HALF YEARS' EXPERIENCE in the repair of atrial septal defects with hypothermia we present this description of our technique hoping that it will prove useful to others interested in this type of surgery. Hypothermia permits repair under direct vision in a bloodless field through the use of relatively simple mechanical aids and it is suitable for patients in a wide range of age and body size.

TECHNIQUE

Preoperatively there has been no unusual preparation. Some of the patients have been digitalized for indications such as auricular fibrillation and congestive heart failure, but digitalization has not been used routinely. Penicillin is given routinely, however, for 24 hours prior to surgery. Edema is treated vigorously in the few patients in whom it exists prior to surgery.

The equipment is assembled and tested with the aid of check-lists which list the special respiratory equipment and the machinery for cooling and warming as well as the operating instruments. Additional check-lists for the immediate preoperative preparation of the equipment and the patient and for the actual operative procedure are also helpful. By trusting these lists rather than memory the whole effort moves along without confusion.

Anesthetic induction with thiopental sodium and intratracheal intubation are carried out while the patient is still on the cart that carried him to the operating room. He is then transferred to the operating table on which lies one of the two large refrigerating blankets which has been cooled to a temperature of about 20 degrees F. Electrocardiograph limb leads are attached by using subcutaneous needles, an electrical thermometer is placed in the rectum, and a polyethylene tube is inserted into the radial artery and attached to a mercury manometer. After covering the patient with wet hand towels, the second refrigerating blanket is laid on top and wrapped around him (Fig. 1A). Cotton blankets over this help to keep the refrigerating blankets cool. Nevertheless, the temperature of the fluid flowing through the refrigerating blankets comes up and levels off at 25 to 30 degrees F. Following these preliminary steps, the intratracheal tube is disconnected from the standard anesthesia machine and attached to an automatic respirator which provides 5 per cent carbon dioxide and oxygen under intermittent, positive pressure at a constant rate and volume.

Adjustments which we make in the blanket temperature, either up or down, are governed by the patient's size and the rapidity of his temperature drop, but the objective has been to reach a low rectal temperature of 83 to 86 degrees F. (28 to 30 degrees C.) at the time the cardiac inflow is occluded and then to rewarm the patient as rapidly as possible. As the temperature drops below 93 degrees F. (33.8 degrees C.) during cooling, the temperature of the blankets may be increased to 60 to 70 degrees F., but the thoracotomy is usually not started until the rectal temperature has fallen to 89 degrees F. (31.6 degrees C.). As soon as the cardiotomy has been completed, the blanket is warmed to 110 degrees F. in order that the rewarming may start while the operation is being completed.

Some additional description of the anesthesia technique is in order, for it differs in some respects from the technique employed by others using hypothermia. We have used intravenous thiopental sodium and flaxedil® (gallamine triethiodide) mixing the two agents in a syringe (25 mgm. of thiopental sodium and 4 mgm. of flaxedil per c.c.), though, occasionally, in the latter part of cooling thiopental has been given alone. These agents have the advantage of being nonexplosive, and they are relatively easy to use. Throughout cooling the patient is kept at a

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This work was supported in part by Grant H-2879 of the United States Public Health Service.

deeper level of anesthesia than would be necessary simply to get him through the operation. Enough anesthesia is given to abolish all visible and palpable muscle tremors or shivering, and this has usually required 30 to 35 milligrams of thiopental per kilogram for the entire procedure. We have tried to avoid muscle activity because the most important benefit of hypothermia—the reduced metabolic rate—is lost if the patient shivers.

The automatic respirator employs a semiopen system rather than the circle absorption system characteristic of most anesthesia machines. It consists of 2 solenoid valves which are controlled by an electronic timing circuit, as described by Turbak and associates. The inspiratory valve opens to a tank of 5 per cent carbon dioxide in oxygen through a pressure reducing valve and an expansion chamber. The expiratory valve (which is closed while the inspiratory valve is open and vice versa) simply leads to the ambient air. By providing a constant minute respiratory volume (12 to 15 liters in adults) throughout the procedure, the patient is hyperventilated at the lower temperature levels. Therefore, if oxygen without carbon dioxide is given, respiratory alkalosis and a high blood hydrogen ion concentration will invariably develop but this is avoided, and the hydrogen ion concentration kept almost constant by simply using a mixture of 5 per cent carbon dioxide in oxygen. As an alternative, the hydrogen ion concentration could be controlled by decreasing the minute respiratory volume as the temperature falls, but this technique is more difficult, and to carry it out properly the respiratory volume should be governed by frequent measurements of the alveolar carbon dioxide. Moreover, if this scheme is employed, serious difficulty is encountered in trying to maintain uniform lung ventilation once the chest has been opened. The temperature will be low at this point, and consequently the minute respiratory volume, as governed by measurements of the alveolar carbon dioxide level, will be small; therefore, segments of the lung are apt to become atelectatic. Unoxygenated blood is shunted through these nonventilated segments without encountering alveolar air. If attempts are made to correct this difficulty by temporarily hyperventilating the lungs, there is a deleterious upward shift in the blood hydrogen ion concentration—a shift which predisposes to ventricular fibrillation. These problems can be avoided by simply using a semiopen, automatic respirator which administers 5 per cent carbon dioxide in 95 per cent oxygen throughout.

During the entire procedure the electrocardiographic pattern is monitored on an oscilloscope (Fig. 1A). Temporary cardiac arrhythmias are relatively frequent in these patients, especially at the lower temperatures, and while the heart is being manipulated. If auricular fibrillation occurs, no special remedy is indicated, but we often give 100 milligrams of procaine amide intravenously if there are runs of ventricular extrasystoles during cooling. If ectopic beats occur during preliminary cardiac manipulation, we desist until a regular beat returns.

When the temperature has fallen to the desired level (approximately 89 degrees F. or 31.6 degrees C.), and with the patient still in the supine position, the top blanket is drawn down to permit exposure for a transverse submammary incision (Fig. 1B). Loops are placed around both cavae and usually around both lung roots (Fig. 1C), but before proceeding to interrupt the circulation the surgeon explores the cardiac chambers by inserting a finger through the right atrial appendage (Fig. 1D).

After preparations have been completed, the cardiac inflow is occluded by tightening the ligatures around the cavae and the lung roots, and the outflow is occluded by clamping the aorta and the pulmonary artery with a Satinsky vena cava clamp, one blade of which is passed through the transverse sinus of the heart.

With the atrium opened widely and the right side of the heart emptied of blood (Fig. 1E), the defect is repaired with a running stitch of No. 00 silk reinforced with 2 or 3 additional interrupted stitches. As pointed out previously (1), the details of the repair depend upon the anatomy of the particular defect. Before the running stitch is tied, air is washed out of the left atrium by injecting saline under pressure through a small metal tube (Adson, neurosurgical, suction tip) (Fig. 1F). The right atrium is filled with blood by releasing the inferior vena cava, and the cardiotomy wound in the atrium is then closed with a large Satinsky clamp as the traction sutures on the edge of the wound are elevated (Fig. 1G). Circulation is resumed before closing the cardiotomy wound with silk.

A firm repair of the chest wound is more difficult in adults than in children, but it can be achieved. A V-shaped rather than a straight

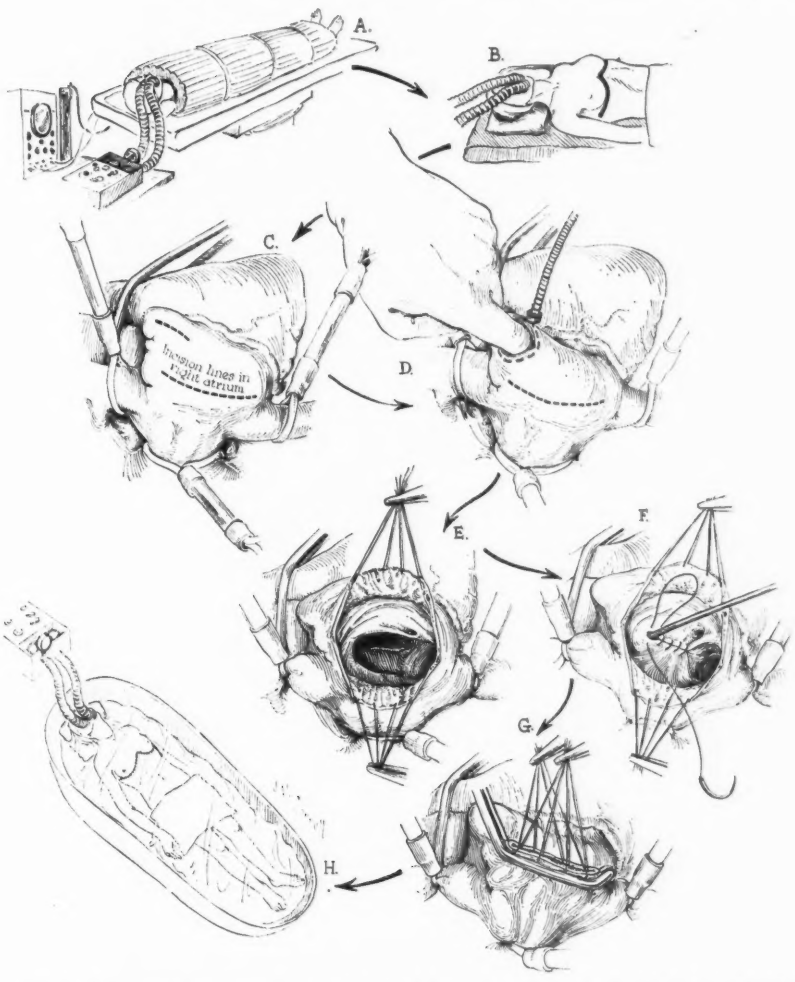

FIG. 1. This illustration shows the steps for repairing atrial septal defects under hypothermia. A, The patient has been anesthetized, intubated, and wrapped in the refrigerating blankets. The automatic respirator, oscilloscope, and arterial manometer are shown at the left. B, The bilateral submammary incision. C, Loops of tape are in place around each cavae and the right lung root, and the sites of the atrial incision are shown. D, Digital exploration is carried out prior to the open cardiotomy. If mitral stenosis is encountered at this time, a commissurotomy is done. E, After cardiac inflow and outflow interruption the right atrium is opened widely to expose a typical foramen ovale defect. F, As the first, continuous, repair suture is about to be tied and the left atrium is filled with saline injected through a small metal tube. G, The atrial incision is closed with a large clamp. After this, circulation is restarted while the incision is being sutured. H, The patient is warmed in a bath of hot water.

transection of the sternum helps, for it allows locking of the sternal fragments. Fixation of these fragments is accomplished with 3 double sutures of heavy, twisted, stainless steel wire, and further stabilization is achieved by using 2 heavy pericostal sutures of catgut on either side.

The method of rewarming employed depends upon the patient's size. By warming the blankets to 110 degrees F. a child's temperature may be brought up while the wound is being repaired, but larger patients will still have a low body temperature after the chest has been closed. They are placed in a bath of hot water (Fig. 1H), at about 112 degrees F. until the body temperature has reached approximately 95 degrees F. Even though rewarming is stopped at this rectal temperature, there will occasionally be an overshoot to 101 to 102 degrees F. in the first few postoperative hours.

After the temperature has reached normal there is nothing unusual in the postoperative care of these patients. Atelectasis may be a troubling complication, and cardiac arrhythmias—usually auricular fibrillation—may come and go. In the early postoperative hours there is some danger of bleeding. We are not certain from our own experience that the tendency to bleed is any greater after these operations than it is after operations of similar magnitude done at normal temperatures; but this sometimes appears to be the case. Frequently, an adult patient will lose 1,000 cubic centimeters of blood through the chest catheters during the first 12 hours postoperatively. All patients have their measured blood loss generously and promptly replaced, for we believe that any drop in blood pressure is best regarded as secondary to bleeding rather than as due to some obscure vasomotor collapse or to heart failure.

DISCUSSION

We have used hypothermia for the direct vision repair of atrial septal defects in 65 patients, and in general, the results, which have been described in another publication (2), have been good. There were 7 operative deaths in this series, although there was only 1 death among the last 21 patients.

The anesthetic technique described in this article, employing an artificial respirator and the administration of a mixture of 5 per cent carbon dioxide in oxygen, has been used for the last 32 patients with only 2 instances of ventricular fibrillation. Among the first 33 patients, on the other hand, manual respiratory control was used, and there were 11 instances of ventricular fibrillation. We believe that the artificial respirator which permits a better control of the blood hydrogen ion concentration level has helped to decrease the risk of serious arrhythmias among these patients. Simultaneously with this change in respiratory technique, however, we have made other changes which might have helped to reduce the incidence of ventricular fibrillation. We have used deeper levels of anesthesia, we have used a slightly higher body temperature (median low temperature of 28.0 degrees C. in the patients with manual respiration and 28.5 degrees C. in the last group who were on the automatic respirator), and we have gained in experience. As is so often the case in clinical medicine, our contention, in this case that automatic respiration is best, has not been established with an adequately controlled study. Nevertheless, the theoretic, experimental, and clinical evidence which we have gathered support the idea, and we plan to continue using an automatic respirator for hypothermia patients.

There are, of course, other ways to repair atrial septal defects, and it is not possible to say that one technique is clearly the best. On the basis of our own experience we cannot compare our open technique with the various closed methods that have been recommended to repair atrial septal defects. We have not tried them. Good results have been obtained with closed techniques, and other surgeons will doubtless continue to use them, at least for a while. But if the operative field can be exposed under direct vision, without undue additional risk, the technique that provides such exposure should represent an advance over closed methods. The current trend in heart surgery unquestionably favors open rather than closed operations. Following the introduction of hypothermia for open operations interest in extracorporeal pump-oxygenators quickened, and they are now widely employed. One may ask if they should not replace hypothermia to repair atrial septal defects, especially after these machines have been perfected and made safer. Pump-oxygenators provide the important advantage of longer operating time while the heart is open. We have not yet used pump-oxygenators clinically to repair atrial septal defects, and there are, as yet, no adequate reports in the literature by others regarding the use of pump-oxygenators to repair significant numbers of this defect.

Doubtless such reports will be forthcoming; still it may take some time before the relative merit of the various possible methods for repairing atrial septal defects—closed, open with hypothermia, and open with pump-oxygenators—is established. It is possible that more than one technique may retain a place in the field.

Hypothermia has some valuable attributes. It allows open repair in a bloodless field without complex equipment, without a special team of assistants, without heparinization of the patient, and without special blood donors. Time limitation is its most important disadvantage. This limitation may be partially overcome by adding selective coronary perfusion or by using lower body temperatures. But we have not felt that either of these changes or that the use of the pump-oxygenators was needed in order to repair most atrial septal defects in an open field.

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THE SURGEON'S LIBRARY

Reviews of New Books

THE VERY COMPREHENSIVE and excellent volume entitled *Chirurgie du pancréas*[1] (Surgery of the Pancreas) is written by two experts in this field. The monograph consists of more than 500 pages and contains many well chosen and clearly reproduced photographs, photomicrographs, drawings, and sketches. The text is well arranged and different types of print render the book very readable; topics of interest are readily found.

The material covered is not merely surgical. Whenever known, there is a thorough discussion of the etiology, pathogenesis, symptomatology, clinical forms, operative diagnosis, methods of treatment (surgical and nonsurgical) of the different disease entities, as well as of their sequelae and prognoses. Case histories are presented to illustrate the different clinical aspects.

The chapters on acute and chronic pancreatitis and cancer of the pancreas are very detailed. The surgical procedures are presented by a concise description and are clearly illustrated. The authors show special interest in diagnostic roentgenology in relation to the pancreas and choledochus, such as pancreatography and direct cholangiography.

The pertinent recent literature of the French, German, Anglo-American language, and others is very well covered. However, in spite of the familiar references, this volume represents not merely a review of the standard issues, but contains many original thoughts.

This book would be of great benefit and ideal for the surgeon whose interests surpass surgical procedures or surgery per se. Many parts would also be of interest to the internist, especially the detailed chapters concerning the diagnosis of the different lesions and the question of medical versus surgical treatment. It is, however, too detailed for the reader interested in a rapid scanning of this field. The language might impose an impediment for many, as a more than average knowledge of a foreign language is necessary to read this well written book with understanding.

—*Herbert K. Beutler.*

THE VOLUME entitled *International Congress of Gastroenterology*[2] incorporates the fifth meeting of the Association of European and Mediterranean societies of gastroenterology held at the Royal College of Surgeons in London, England, from July 18 to 21, 1956. The session opened with a series of papers on the subject of nonmalignant conditions of the esophagus, continued with a series on premalignant conditions of the gastrointestinal tract, and ended with papers on ulcerative colitis. All of the papers are collected in book form as a full record of the proceedings of this international congress of gastroenterology. The volume is concerned with the many aspects of gastroenterology and includes the writings of distinguished authors in many special subjects from many different countries. An excellent cross section of gastrointestinal knowledge and interest in the European and Mediterranean areas, as well as in the United States, is presented in this volume.

—*Clifford J. Barborka.*

THE VOLUME edited by Emil A. Naclerio[3] presents a detailed discussion of modern day concepts in the diagnosis, treatment, pathology, physiology, and anatomy of the bronchopulmonary system and its diseases. Some 142 authors have contributed to the book. All are experts in their fields and each has presented an authoritative discussion of his subject. Each of the sections is not only complete in itself with respect to the subject material presented but is also linked logically with the subjects presented in other chapters and sections of the volume. Each author has succeeded in maintaining a concise writing style and has also provided a precise accounting of his subject material. As a result, the volume serves not only as a reference work and as a review of the basic concepts of physiology, anatomy, and pathology of the bronchopulmonary system but also as a guide to diagnosis and therapy.

The first section of the volume is devoted to the basic considerations of anatomy, pathophysiology, and bacteriology as each of these relates to diseases or malformations of the bronchopulmonary system. Especially important are the pages which present the value of lung biopsy in disseminated pulmonary disease. The place which bronchoscopy holds in the management of bronchopulmonary diseases is admirably discussed.

[1]CHIRURGIE DU PANCRÉAS. By Lucien Leger and Jacques Brehant. 504 pages, 154 illustrations. 4.800 fr. Paris: Masson et Cie, 1956.

[2]INTERNATIONAL CONGRESS OF GASTROENTEROLOGY. Fifth meeting of L'Association des Sociétés Européennes et Méditerranéennes de Gastro-Entérologie. London, July 18–21, 1956. 634 pages, illustrated. Basel and New York: S. Karger, 1957.

[3]BRONCHOPULMONARY DISEASES; BASIC ASPECTS, DIAGNOSIS AND TREATMENT. By 142 authors. Edited by Emil A. Naclerio, M.D. 956 pages, 719 illustrations. $24.00. New York: Paul B. Hoeber, Inc., 1957.

An important section of the volume is devoted to roentgenology. This is a most valuable part of the book and the subject is presented in considerable detail. The many black and white drawings of representative roentgenograms depicting different disease processes are most helpful in the understanding of not only the roentgenographic appearance of such diseases but also the disturbed anatomy and physiology associated with these conditions.

Another part of the book deals with the relationship of bronchopulmonary diseases in conditions affecting the heart and great vessels. Diseases of the pulmonary-arterial system, including pulmonary embolism, infarction, edema, and hemorrhage, are discussed in this section.

Other subjects presented include the use of steroid compounds in the treatment of bronchopulmonary disease, and the present surgical management of coin lesions, decortication of the lung, injuries of the lung, and disorders of the bronchi and trachea. The section on primary cancer of the lung is an excellent one and is skillfully presented. The problems of pyogenic abscess, segmental resection of the pulmonary parenchyma, and the diagnosis and treatment of tuberculosis are also described in this section. Current concepts in the management of pulmonary tuberculosis and the value of various medical and surgical procedures are assessed with reference to the resistance of tubercle bacteria, the severity of the disease, and the relationship between the conservative and the more radical approaches to this problem.

A review of a book such as this is an easy task. Valuable information has been assembled by a thoughtful and diligent editor from magnificent contributions by recognized experts in the field of bronchopulmonary disease. Such expert efforts must of necessity culminate in a superb volume. These authors have succeeded exceptionally well in presenting in textbook form the modern principles of treatment of the many problems associated with bronchopulmonary disease.

Although the concepts in management of diseases of the bronchopulmonary system seem to change rapidly, this volume will be an enduring one. The editor and the contributors have stressed the basic principles underlying the diagnosis and treatment of these disorders and have avoided discussions of controversial methods of therapy. For any physician interested in diseases of the bronchopulmonary system this volume should be one of the most valuable books on his reference shelf. —*Orville F. Grimes.*

THE VOLUME entitled *Pneumoencephalography*[4] should be considered a classic in neurosurgical, neurologic, and radiologic literature. Starting with the table of contents, which is clear, descriptive, and complete to enable ready reference for particular problems, and continuing through 28 chapters to the references and index, the detail, makeup, literary style, illustrations, and choice of type enable informative and pleasant reading.

It is the reviewer's belief that lettering of the illustrations would be helpful as well as an improvement. As it is, one cannot readily determine which is A, B, or C. This detracts somewhat from the references to the illustrations.

The introductory chapter describes simply the history of the development of pneumoencephalography and credits important contributions without going into boring detail. Chapter 2, on the "Distribution of Gas," should be carefully read by anyone who is interested in the mechanisms and the reasons for the findings in pneumoencephalography. The factors to be considered in the principles of pneumoencephalography, the basic technique, and reasons for success or failure are carefully analyzed in 4 chapters. One chapter, each, is utilized for discussion of the third ventricle, the aqueduct of Sylvius, the third ventricle and cisterns, the pathologic appearances of the third ventricle, the suprasellar region, the lateral ventricles, and the lateral ventricle deformities by neoplasm. The clinical entities and the pneumoencephalographic findings are carefully analyzed.

While case histories are used for description, they are not repetitious or monotonous. The illustrations of the anatomic specimens and roentgenograms which accompany or are a part of each point of discussion are exceptionally clear, descriptive, and informative. The use of pictures or drawings to illustrate the position of the patient and relation of the x-ray appartus should be very helpful to the encephalographer. Since reading this monograph very carefully, the reviewer believes that he has improved his encephalographic technique.

In summary, as before stated, the reviewer believes that a classic monograph has been added to the medical literature, and one which could be a basic text for anyone interested in pneumoencephalography.

—*David Cleveland.*

THE NEW EDITION of *Extensile Exposure*[5] by Arnold K. Henry continues to give evidence of the laudable dependence of a surgeon upon the facilities of the dissecting room; the new volume represents the kind of textual and pictorial product which the reader might expect to emanate from the Royal College of Surgeons of Ireland.

The book is written in a style which combines scholarship, technical knowledge, and a stimulating, at times even chatty, style. The pictures are original in conception, helpful in content.

The new edition is almost double the size of its predecessor. A great deal of new material has been added to cover exposure of the long bones, the surgical anatomy of the neck, thoracic inlet, lungs, and thoracic division of the sympathetic chain. True to the implications of the title of the volume, Henry advises long incisions, with respectful avoidance of areas traversed by cutaneous nerves.

The semischematic figures immediately attract the reader's attention. Notable for their possible service are those which depict the morphologic basis for stripping angle at sites of osseomuscular fusion, the muscular gutter for cephalic vein, the disposition of

[4]PNEUMOENCEPHALOGRAPHY. By E. Graeme Robertson, M.D. (Melb.), F.R.C.P., F.R.A.C.P. 482 pages, illustrated. $14.50. Springfield, Ill.: Charles C Thomas, 1957.

[5]EXTENSILE EXPOSURE. By Arnold K. Henry, M.B., Dublin; M.Ch. (Hon.) Trinity College, Dublin, and Cairo; F.R.C.S.I. 2nd Ed. 326 pages, illustrated. $10.00. Baltimore: Williams & Wilkins Co., 1957.

the infraclavicular fascia, sites for fingerbreadth measurements in vertebral surgery, position and extent of intermuscular "seams" and planes of cleavage, and utilization of the hand to indicate the positions of deeply placed vessels and nerves.

Nomenclature in parts of the book may present a lesser stumbling block to those who have received their medical education in the United States, where a stout effort has been made to adhere to the Basle (BNA) terminology. However, since even the latter is in a state of carefully superintended, sometimes unrewarding, flux, Professor Henry's decision to use names which custom sanctions is certainly defensible. Even the retention of personal names in nondescriptive association with human structures is forgivable when the inadequacy of the present day term is made clear. To select a single example Henry employs "space of Retzius" for the abdominopelvic interval of which the retropubic component is but a part—broadening his conversational presentation to include the ground plan of the area, its boundaries, septa, and adherent structures encountered in the course of surgical exploration.

Altogether, the volume, *Extensile Exposure*, is a desirable book; it is readable, energizing, and instructive. Throughout the volume, Arnold Henry's handling of his subject carries the conviction of maturity in the allied fields of pedagogy and surgical handicraft. —*Barry Anson.*

THE AIM of the authors and publisher of the book entitled *Operative Obstetrics*[6] was to make it a companion to *Williams' Obstetrics*. The authors believe their book is necessary because the refinements and pitfalls in obstetric surgery cannot be described nor detailed adequately either in an atlas or in a general textbook of obstetrics. Furthermore, they maintain that it is impractical today to include the details of many operations, as well as the necessary procedures, in a comprehensive text on obstetrics. In conformity with this belief, the chapter on "Forceps" contains more than 200 illustrations. In some instances the allotment of illustrations is disproportionate. There are 16 illustrations for appendectomy, but only 7 show the use of local infiltration anesthesia for cesarean section. Also, there are 10 illustrations for paravertebral anesthesia, even though this form of anesthesia alone or in combination with other types of anesthesia was employed only 250 times in 12,355 deliveries at the New York Hospital. Local anesthesia, usually with other forms of anesthesia, was used in about 6,000 cases.

In the discussion on therapeutic abortion, the authors properly condemn the use of irradiation for the purpose of interrupting pregnancy. In the section on induction of labor, the bougie and balloon are described, but the authors have not used either of these procedures for many years.

The authors strongly advise the use of axis-traction forceps whenever indicated and the more frequent use of the Kjelland and Barton forceps in tranverse and posterior positions. They say the old adage "learn to use one type of forceps" no longer has a place in modern obstetrics. They attempt external cephalic version during the last few weeks of pregnancy for correction of breech presentation, except when confronted with certain contraindications, such as premature rupture of the membranes, engagement of the breech in the pelvis, previous classical cesarean section, and other reasons.

The low cervical cesarean section is the preferred operation, except for the occasional indication for cesarean hysterectomy or extraperitoneal operations.

This is an excellent book, and the authors have accomplished their aim in a magnificent manner. The text is well written in a lucid style. The advice given is practical and authoritative because it is based on the extensive experience of the authors as obstetricians, teachers, and investigators. The illustrations are beautiful, clear, and instructive; most of them are the work of such great medical artists as Elizabeth H. Broedel and Emily M. Freret. The lists of references are complete and up to date. The paper is sturdy, the type is clear, and the book is well bound. Both the authors and the publisher are to be congratulated on this outstanding book. —*J. P. Greenhill.*

ONE OF THE CONTRIBUTORS to the book, *Management of Complications in Eye Surgery*,[7] quotes the adage: "The only surgeon who does not have to deal with complications is one who does not operate." Most textbooks of ocular surgery devote only a paragraph or two to complications at the close of each chapter, and this text is an attempt to amplify these apologetic paragraphs and present them in an orderly fashion.

There are 3 introductory chapters on the anesthetic, medical, and psychiatric complications of ocular surgery. Except for the specific references to regional anesthesia about the eye, this section may be read with profit by all surgeons. The succeeding chapters are devoted to complications of the various operations performed by ocular surgeons. Each chapter is written by an authority in the field, so that there is a wide variety of presentations. For example, Thorpe's chapter on intraocular foreign bodies is a complete "how-to-do-it" exposition on the management of such injuries, while Kronfeld limits himself to a discussion of one complication of intraocular surgery, the flat anterior chamber.

This main corpus of the book is followed by a concluding section of topics that are not strictly surgical complications. These include endocrine exophthalmos, rehabilitation of the low vision patient, and a reproduction of a report of a committee of the Council on Industrial Health on estimation of loss of visual efficiency. Although in a sense extraneous to the premise of the book, this is one of the most valuable sections thereof and a "must" for all surgeons who are required to evaluate industrial visual disability.
—*David Shoch.*

THE GROUP of distinguished Scandinavian surgeons who planned the first congress and the organization of the International Society of Plastic Surgeons and

[6]OPERATIVE OBSTETRICS. By R. Gordon Douglas and William B. Stromme. 735 pages, 859 illustrations. Price $20.00. New York: Appleton-Century-Crofts, Inc., 1957.

[7]MANAGEMENT OF COMPLICATIONS IN EYE SURGERY; AVOIDANCE OF PITFALLS AND TREATMENT OF DIFFICULT SITUATIONS IN OPHTHALMOLOGIC OPERATIONS. Edited by R. M. Fasanella, M.D. 422 pages, illustrated. $16.00. Philadelphia and London: W. B. Saunders Co., 1957.

particularly their secretary, Dr. Tord Skoog,[8] deserve great credit for the well written and well illustrated report of that congress. The wide range of subjects covered is indicated by the twelve chapter headings: Burns, Cleft Lip and Palate, Jaws, Nose, Eye, Ear, Scalp and Cranium, Oesophagus, Breast and Abdomen, Genitals, Hand, Clinical and Experimental Research. Two concluding chapters are devoted to miscellaneous conditions and motion pictures.

The first two chapters, on Burns with twenty-nine presentations, and Cleft Lip and Palate with eighteen, comprise well over one-third of the volume. The remaining chapters are of fairly equal length with presentations varying in number from two (Scalp and Cranium) and three (Oesophagus) to eight (Hand) and eleven (Clinical and Experimental Research). Each presentation is written in English, and is followed by abstracts in French, German, and Spanish. This feature alone makes one realize how much thought and effort have been expended in preparing these transactions for publication.

The majority of the papers presented are illustrated, some profusely, and the illustrations are reproduced with unusual clarity. Not the least interesting feature of the volume is the group of photographs of many of the distinguished participants in the congress and of their wives.

It would be difficult, perhaps unfair, to select from so many admirable presentations any for special comment. The importance of the burn problem is stressed by the space that has been allotted to it. Blocker's discussion of treatment in the event of mass disaster, Jackson's (of Birmingham, England) paper on early excision and grafting of extensive deep burns, Muir and Grummit's (of Norwood, England) paper on the same subject, Skoog's discussion of homografting and skin storage, accompanied by excellent illustrations, Troll's (of Stockholm) estimation of red cell destruction in burns, the report of Lieutenant Colonel Curtis Artz and his group of Fort Sam Houston, Texas on fatal septicemia in severely burned patients are all of great interest to every worker concerned with the burn problem. A number of well illustrated papers on the treatment of burn contractures adds further interest to this section.

The report of these transactions in their entirety provides a comprehensive view of the variety and difficulty of the many problems that confront the plastic surgeon and of how men in widely separated world areas are attacking those problems.

—*Sumner L. Koch.*

THE LATEST ADDITION to the John Alexander monographs on thoracic surgery is a practical book entitled *The Postoperative Chest*[9] which will be appreciated chiefly by men working in small communities where only a small amount of thoracic surgery is done. It shows the roentgenographic appearance of the chest after various thoracic operations, and shows them clearly. There are line drawings which serve to interpret the roentgenograms. The rather bizarre changes that appear in the x-ray examination of the chest following thoracic operations, and which are the result of normal changes, are well known to those experienced in thoracic surgery, or in the interpretation of roentgenograms taken after thoracic operations. The roentgenologist unfamiliar with these normal changes will see evidences of pneumonia, atelectasis, and fluid formation, and will not know the explanation for these findings. Even men well trained in general roentgenology will be puzzled by these changes which occur so frequently. This book, therefore, should prove of great value, and should help raise the quality of thoracic surgery throughout this country.

Very few books are perfect and this one has one defect. Occasionally the time period after operation is not given. This volume should be in the hands of all who do occasional chest operations, and especially in the hands of the roentgenologists who work with them. For men who are experienced chest surgeons and the roentgenologists associated with them, the book will prove interesting. To the teacher of chest surgery it should be very valuable. —*Richard H. Meade.*

A DETAILED OUTLINE of a closed method of treatment for a certain type of fracture in adults characterized by (1) difficulty in reduction and (2) difficulty in maintaining adequate reduction is given in *Die Diafixation ein Verfahren zur versorgung schwer Einrichtbarer und zu Verschiebung Neigender Schaftrurche.*[10] The material is presented very thoroughly, and includes the history and development of different methods of handling these fractures, a discussion of the basic principles upon which the proposed treatment is based, problems of anesthesia, the technique of reduction and fixation, a discussion in detail of the different types of fractures, and illustrative case reports. There is also a detailed bibliography of both the European and American literature.

Diafixation is derived from the Greek *dia* and the Latin *fixation* and describes precisely the important feature of the method, namely fixation of the bone fragments by means of a pin at a right angle to the fracture plane or as close as possible to it, the pin transfixing both fragments. Provided the pin is placed accurately it constitutes the ideal way indeed of counteracting the tendency toward oblique displacement which is present in the fractures under discussion. One pin is usually sufficient to maintain reduction securely. The author considers this to be a closed method and rightly so, even though it must be admitted that the pin traverses the fracture hematoma. The author's incidence of infection is almost negligible.

The technique is simple and consists of: (1) closed reduction with or without the use of what amounts to

[8] TRANSACTIONS OF THE INTERNATIONAL SOCIETY OF PLASTIC SURGEONS. First Congress (Stockholm and Uppsala-1955). Edited by Tord Skoog, M.D., with the help of others. 568 pages, illustrated. $20.00. Baltimore: The Williams & Wilkins Co., 1957.

[9] THE POSTOPERATIVE CHEST; RADIOGRAPHIC CONSIDERATIONS AFTER THORACIC SURGERY. By Hiram T. Langston, M.D., Anton M. Pantone, M.D., and Myron Melamed, M.D. 228 pages, illustrated. $8.00. Springfield, Ill.: Charles C Thomas, 1958.

[10] DIE DIAFIXATION EIN VERFAHREN ZUR VERSORGUNG SCHWER EINRICHTBARER UND ZU VERSCHIEBUNG NEIGENDER SCHAFTBRUECHE. By Dozent Dr. K. Pap. 252 pages, 124 illustrations. Budapest: Verlag der Ungarischen Akademie der Wissenschaften, 1956.

a modified Thomas wrench, a very ingenious instrument which gives excellent leverage; (2) temporary skeletal traction if necessary to obtain reduction; (3) insertion of a modified Kirschner wire.

Open reduction is very rarely necessary. Fluoroscopic control is essential, and this may constitute the only, but serious, objection to the method, especially among orthopedic surgeons in this country. Fluoroscopy, however, should not constitute a hazard if all precautions are very strictly observed and adhered to.

Internal fixation by means of one or more pins is not new in itself, but the method of *diafixation* differs in as much as its objective is not merely to pin a smaller fragment to the main part of a bone but to secure complete stability by transfixing the two main fragments of a shaft fracture with a single pin at a carefully calculated angle. At the same time, it is a technical perfection of various methods which have been and are in use in a more or less haphazard fashion. The presentation of this method is accompanied and supported by carefully evaluated statistics based on 416 cases.

The paper and print are excellent, as are the many drawings and roentgenograms. The book is written in German, and the language is perfectly clear and easy to follow. —*G. M. Doerr.*

A FINELY WRITTEN and pleasing group of 5 essays having to do chiefly with the historical aspects of the study of the blood constitute the volume *Some Milestones in the History of Hematology.*[11] No tinge of pedantic historiography or self-conscious antiquarianism mars these essays. They are connected in part by the subject of blood and also by occasional reminders that the evolution of knowledge of disease is not steady growth, but an episodic and discontinuous process. The first essay gives a brief sketch of the development of knowledge about blood; 3 essays deal specifically with the topics of hemolytic jaundice, leukemia, and plethora vera; a thumbnail biography of Georges Hayem concludes the collection. Illustrations are numerous, informative, and excellently reproduced. The little book itself should delight the hematologist, the internist, or surgeon, and perhaps most important, the medical student. —*Edward D. Churchill.*

[11]SOME MILESTONES IN THE HISTORY OF HEMATOLOGY. By Camille Dreyfus, M.D. Foreword by Sir Lionel E. H. Whitby. 87 pages, illustrated. $4.50. New York and London: Grune & Stratton, Inc., 1957.

ERRATUM.—The Editors regret that in the review of *Orthopedic Surgery in the Mediterranean Theater of Operations* which appeared in the April issue of the Journal, page 507, the name of Oscar P. Hampton, Jr. as author was inadvertently omitted.

Dr. Mather Cleveland, Editor for Orthopedic Surgery of the monographs on *Surgery in World War II*, published by the Medical Department of the United States Army, has called our attention to the fact that Dr. Hampton deserves the credit for the authorship of this volume.

BOOKS RECEIVED

BOOKS received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

PHARMACOLOGY IN MEDICINE: A COLLABORATIVE TEXTBOOK. Edited by Victor A. Drill, Ph.D., M.D. 2nd ed. 1273 pages, illustrated. $19.50. New York, Toronto, London: McGraw-Hill Book Co., Inc., Blakiston Division, 1958.

AN INTRODUCTION TO EXPERIMENTAL SURGICAL STUDIES. By W. J. Dempster, F.R.C.S. 463 pages, illustrated. $10.00. Springfield, Il.: Charles C Thomas, 1958.

WIEDERHERSTELLUNGSHIRURGIE UND TRAUMATOLOGIE (RECONSTRUCTION SURGERY AND TRAUMATOLOGY); ANNUAL SURVEY. Edited by M. Lange. Vol. IV. 222 pages, 201 illustrations. $13.75. Basel (Schweiz): S. Karger; White Plains, N. Y.: Albert J. Phiebig. 1957.

HUMAN INFERTILITY. By C. Lee Buxton, M.D., and Anna L. Southam, M.D. With a chapter on Endometrial Diagnosis by Earl T. Engle, Ph.D. 229 pages, illustrated. $7.50. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1958.

HEART DISEASE IN INFANCY AND CHILDHOOD. By John D. Keith, M.D., Richard D. Rowe, M.B. (N.S.), F.R.C.P. (Edin.), and Peter Vlad, M.D. 877 pages, illustrated. $22.50. New York: The Macmillan Co., 1958.

A HANDBOOK OF OPERATIVE SURGERY; SURGERY OF THE CHEST. By Julian Johnson, M.D., D.Sc.(Med.), and Charles K. Kirby, M.D. Illustrated by Edna Hill. 2nd ed. 398 pages, illustrated. $9.75. Chicago: The Year Book Publishers, Inc., 1958.

RECONSTRUCTIVE AND REPARATIVE SURGERY. By Hans May, M.D., F.A.C.S. 2nd ed. 1115 pages, 1030 illustrations (55 in color). $30.00. Philadelphia: F. A. Davis Co., 1958.

NEOMYCIN; ITS NATURE AND PRACTICAL APPLICATION. Edited by Selman A. Waksman, assisted by Hubert A. Lechevalier, Burton A. Waisbren, and Robert A. Day. Published for The Institute of Microbiology, Rutgers University. 412 pages, illustrated. $5.00. Baltimore: The Williams & Wilkins Co., 1958.

SOCIEDAD ARGENTIAN DE UROLOGIA. VI Congreso Americano y III Argentino de Urologia, Mar Del Plata 2 al 7 de Diciembre de 1956. Discursos y Temas Libres. 610 pages, illustrated. Buenos Aires: Editorial L.E.Y.C.A., Nocito & Rañó, 1957.

AMERICAN COLLEGE OF SURGEONS

WILLIAM L. ESTES, JR., Bethlehem, Pennsylvania, *President*
NEWELL W. PHILPOTT, Montreal, Canada, *President-Elect*

PRELIMINARY PLANS FOR THE 44th CLINICAL CONGRESS THE CONRAD HILTON HOTEL, CHICAGO, ILLINOIS OCTOBER 6 TO 10, 1958

MARKING 121 lusty years as of March 1958, Chicago's place in the health world has kept pace with the dynamic growth of the city. Chicago is now headquarters for numerous medical and allied organizations, home of 5 medical schools, 3 dental schools, unsurpassed hospital and research facilities, 69 approved hospitals, and expanding medical centers.

Visitors to the forty-fourth annual Clinical Congress, the twelfth to be held in Chicago, will find this bustling hub city of the nation hospitable to its guests and eager to display its medical progress. Headquarters will be The Conrad Hilton. All registration, and the major part of the principal scientific and technical exhibits, postgraduate courses, and forum reports will be scheduled here. Closed circuit television programs will originate from Passavant Memorial Hospital.

The Congress program will unfold in this Journal as it develops, with the final program to be published in the September issue. The general plan of the Congress will follow that of previous years.

The student program of College sponsorship of a week of study for outstanding medical students will be continued, headed by Dr. George V. Brindley, Temple, Texas.

The Baxter Lectureship

The Baxter lectureship, innovated last year, and endowed by the Baxter Laboratories of Morton Grove, Illinois, will present Dr. Gunnar Thorsen, of Stockholm, Sweden, renowned in the field of parenteral fluid therapy.

Chicago Committee on Arrangements

Dr. Robert L. Schmitz, Chicago, Associate Clinical Professor of Surgery at Loyola University, is Chairman of the Advisory Committee on Local Arrangements. Dr. Frederick W. Preston, Chicago, Assistant Professor, Northwestern, Chief of Service, Veterans Research Hospital, is Secretary. Serving under Dr. Schmitz are the following local Fellows of the College:

CORNELIUS M. ANNAN
M. FLETCHER AUSTIN
JOHN L. BELL
WALTER W. CARROLL
DWIGHT E. CLARK
JOHN B. CONDON
DAVID N. DANFORTH
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The Press Relations Committee follows:

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T. HOWARD CLARKE
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PAUL V. HARPER
PETER V. MOULDER
WILLIAM L. RIKER
CHARLES A. SCHIFF

Dr. Walter W. Carroll, Associate Professor of Surgery at Northwestern University, and Dr. J. Garrott Allen, Professor of Surgery, University

of Chicago, and Chairman of the College's Committee on Television, are in charge of the television program.

Official Meetings

On the opening evening, Monday, Dr. Schmitz will welcome visitors to the Congress, Dr. Ravdin will introduce special guests, and the Martin Memorial Lecture will be heard. On Friday evening, Initiates will be presented for fellowship, honorary fellowships conferred, and new officers inaugurated. Dr. Newell W. Philpott, incoming President of the College, will give the Presidential Address.

Television, Ciné Clinics, Motion Pictures

Smith, Kline & French Laboratories, producers of the famous closed-circuit operative telecasts, will again bring surgery as it is being performed, this year from Passavant Memorial Hospital in Chicago. The outstanding color film lectures known as Ciné Clinics, sponsored by the Surgical Products Division of American Cyanamid Company, under the chairmanship of Dr. Hilger Perry Jenkins, Chicago, and the College's Motion Picture Committee, will feature new films made for this Congress. Medical motion pictures made by Fellows throughout the country, and approved by the College's Motion Picture Committee, will be a continuing feature of the meeting. The Wednesday evening Motion Picture Symposium will again consist of short films with the operating surgeon explaining the procedures.

Postgraduate Courses

The Postgraduate Courses, always a major attraction at the Congress, have been increased to 9 this year, with the addition of a course in pediatric surgery. Because of the popularity of these classes, it is strongly recommended that you register as soon as possible. Admission will be by ticket only. Courses are:

Preoperative and Postoperative Care. DAVID V. HABIF, New York.

Gastrointestinal Tract. JOHN M. WAUGH, Rochester, Minnesota.

Diseases of the Liver, Biliary Tract, and Pancreas. WILLIAM D. HOLDEN, Cleveland.

Cardiovascular Surgery. ORMAND C. JULIAN, Chicago.

Complex, Complicated, and Combined Injuries. OSCAR P. HAMPTON, JR., St. Louis.

Gynecology and Obstetrics. M. EDWARD DAVIS, Chicago.

Injuries and Other Disabilities of the Hip. HAROLD A. SOFIELD, Oak Park.

Surgical Aspects of Pulmonary Disease. EDWARD M. KENT, Pittsburgh.

Problems in Pediatric Surgery. WILLIS J. POTTS, Chicago.

Forum on Fundamental Surgical Problems

The latest research, changes, and advances in surgical techniques will be presented in this year's expanded Forum program of 16 general and 6 specialty sessions. Dr. Harris B. Shumacker, Jr., Indianapolis, and the Forum Committee will present approximately 250 reports.

Scientific and Technical Exhibits

The Scientific Exhibition Committee, headed by Dr. George W. Stephenson, Assistant Director of the College, has selected informative displays showing new results of study by research teams and surgical departments from medical centers.

Mr. Thomas E. McGinnis, Assistant Business Manager for the Clinical Congress, is in charge of Technical Exhibits, and all inquiries regarding applications and space may be addressed to him at the American College of Surgeons' Chicago headquarters, 40 East Erie Street, Chicago 11.

Advance Registration

The Clinical Congress special Invitation Brochure, containing information about hotels, Postgraduate Courses, travel, and registration forms, has been sent to Fellows, and will be mailed to non-Fellows upon request. Early registration is strongly recommended for first choice at courses and hotel and travel accommodations. Also, anyone registering in advance will find his badge awaiting him upon arrival at the Congress and will avoid waiting in line.

Fellows whose dues are paid to December 31, 1957, pay no registration fee; those whose dues are not paid up to date pay $20.00. Non-Fellows pay $20.00; members of the Federal Services, $10.00. No fee (except for Postgraduate Courses) is required of Initiates, members of the Candidate group, and surgical residents. Everyone who attends a Postgraduate Course pays $5.00.

Wives Invited

The Ladies' Entertainment Committee is planning a week of unusually pleasant activities, and doctors' wives are cordially invited.

CONTRIBUTORS TO VOLUME 106

ADAMSON, J. E., 257
ALLEN, WILLIAM E., JR., 63
ALVES, ALZIR B., 233
ANDERSEN, JAMES G., 679
ANDREWS, RICHARD E., 623
ANSON, BARRY J., 385
ARGUEDAS, J. M., 671
AULT, GARNET W., 467

BARNES, W. A., 337
BARNES, WILLIAM H., 49
BARNETT, WILLIAM O., 38, 511, 667
BEAHRS, OLIVER H., 573
BEATON, LINDSAY E., 385
BENSON, RALPH C., 527
BERG, ELLIOT H., 713
BEUTLER, ERNEST, 734
BICK, EDGAR M., 343
BILL, ALEXANDER H., JR., 643
BLACK, MAURICE M., 163
BLAISDELL, FRANK W., 699
BLAISDELL, PAUL C., 485
BOLLMAN, JESSE L., 306
BOLMAN, R. MORTON, 741
BOREADIS, ANTHONY G., 242
BOYAN, C. PAUL, 207
BOYD, J. F., 176
BRUWER, ANDRE J., 179
BURNETT, W. EMORY, 1

CAMPBELL, GILBERT S., 333
CARRINGTON, ELSIE R., 1
CARTON, CHARLES A., 743
CARVER, GORDON MALONE, JR., 77
CASWELL, H. TAYLOR, 1
CATE, WILLIAM R., JR., 25
CHANG, CHU H., 15
CHESKY, V. E., 70
CLAGETT, O. THERON, 347, 409
CLARKE, B. G., 363
COHN, ROY, 699
COLE, F. H., 196
COLLETT, HUGH S., 623
COLWILL, JOHN C., 713
COOLEY, DENTON A., 615
COON, W. W., 129
COOPER, FREDERICK W., JR., 399
CRILE, GEORGE, JR., 739

DAHLIN, DAVID C., 536
DALE, W. ANDREW, 271
D'ANGELO, GEORGE J., 87
DAVIS, JAMES S., 555
DAVIS, LEONARD, 567
DEARING, WILLIAM H., 145
DEMETRAKOPOULOS, N. J., 729
DEVINE, KENNETH D., 573
DINEEN, PETER, 453
DOCKERTY, MALCOLM B., 347
DONALD, DAVID E., 111
DUNPHY, J. ENGLEBERT, 353

ECK, RICHARD V., 427
EDWARDS, JESSE E., 49
EISENHAMMER, STEPHEN, 595
ELLIS, F. HENRY, JR., 49, 179
ENGLE, MARY ALLEN, 502
ENQUIST, IRVING F., 153
ERICH, JOHN B., 481
EVANS, JOSEPH P., 600

FLICK, FERDINAND H., 321
FLUHMANN, C. FREDERIC, 715
FONKALSRUD, ERIC W., 709
FOSS, EDWARD L., 652
FRIEDELL, MORRIS T., 239

GAFFNEY, CALDWELL J., 63
GARAMELLA, JOSEPH J., 679
GARDNER, W. JAMES, 724
GATCHELL, FRANK G., 347
GERSHON-COHEN, J., 242, 478
GHORMLEY, RALPH K., 536
GILCHRIST, R. K., 631
GINN, B. H., 196
GLIEDMAN, MARVIN L., 153
GREENE, R. R., 413, 729
GRIFFIN, JAMES C., 38
GRINDLAY, JOHN H., 306
GRINNELL, ROBERT S., 288
GURDJIAN, E. S., 412

HAGERTY, ROBERT F,. 119
HALL, BYRON E., 459
HALL, THOMAS D., 233
HALLENBECK, GEORGE A., 306
HANKS, EDGAR C., 207
HANLON, C. ROLLINS, 613
HARDER, R. ALLAN, 271
HARDIN, CREIGHTON A., 82, 605
HARDY, JAMES D., 38
HARDY, William M., 695
HARPER, HAROLD A., 577
HARPER, PAUL V., 600
HARROWER, HAROLD W., 293
HARSHBARGER, HARRY G., 111
HART, DERYL, 257
HEATON, LEONARD D., 484
HELLWIG, C. A., 70
HERSHEY, FALLS B., 63
HODGSON, P. E., 129
HOLSWADE, GEORGE R., 502
HOLTZ, FRED, 639
HOOD, R. MAURICE, 749
HOOD, THOMAS K., 623
HOWLAND, WILLIAM S., 207
HUMPHREYS, ELEANOR M., 600
HUNT, CHARLES F., 516
HURWITT, ELLIOTT S., 743
HURWITZ, ALFRED, 293
HUSNI, ELIAS A., 627

INGLEBY, HELEN, 478

JOHNSON, ROBERT J., 643

KEENAN, HUGH C., 573
KELLY, WILLIAM A., 600
KEMPNER, Ivan, 549
KIESEWETTER, WILLIAM B., 11
KIRKLIN, JOHN W., 49, 111, 179
KRAMER, WILLIAM M., 427
KRAUEL, KATHRYN K., 559

LABERGE, MARTIN Y., 695
LANCE, EDWARD M., 25
LEADBETTER, WYLAND F., 363
LEARNER, NORMAN, 1
LEITHAUSER, DANIEL J., 100
LEMMEN, LLOYD J., 555
LEVEEN, HARRY H., 368
LEWIS, F. John, 610, 751
LIDDLE, GRANT W., 25
LOGAN, WILLIAM D., JR., 399
LOWMAN, ROBERT M., 567
LUDINGTON, LOUIS G., 519

MACDONALD, IAN, 227
MACKENZIE, J. W., 129
MADSEN, E. THYGE, 216
MALLET-GUY, P., 747
MARTIN, WILLIAM L., 105
MARX, RUDOLPH, 375
MAYO, CHARLES W., 695
MCEACHEN, D. G., 655
MCEVOY, RICHARD K., 271

McGarity, William C., 399
McGoon, Dwight C., 409
McParland, Felix A., 11
Menguy, Rene B., 306
Meredith, Donald, 610
Miller, Edwin M., 355
Moertel, Charles G., 652
Moore, D. F., 655
Moore, Lolita, 478
Morgan, Perry, 605
Morgenstern, Leon, 545
Mowlem, Albert, 333
Munnell, Equinn W., 321
Murdaugh, H. V., Jr., 87
Myers, William H., 239

Najarian, John S., 577
Nanson, E. M., 655
Neely, William A., 667
Newman, Ernest B., 687
Newman, Herbert F., 687
Niazi, Saud A., 751
Northup, Jane D., 687

Olmstead, Edwin G., 41
Oropeza, Reuben, 679

Papper, E. M., 207
Parks, Ralph D., 413
Parsons, Willard H., 435
Payne, J. Thomas, 559
Pearce, Charles, 453
Pearse, Herman, E., 97
Perdue, Garland D., 586
Pérez-Tamayo, R., 671
Phillips, Donald F., 145
Postlethwait, R. W., 257
Pratt, George F., 536
Pressman, Joel J., 56
Pritchard, Jack A., 516
Prudden, John F., 702
Pualwan, Fawzi, 358
Putong, Paul B., 489

Ravitch, Mark M., 619
Redo, S. F., 337
Reeves, Melvin M., 610
Riddell, Orin, 199
Roth, Donald A., 41
Rubricius, Jeanette L., 368
Rudy, Harold A., 363

Sabiston, David C., Jr., 709
Scheerer, P. Philip, 413
Schell, Robert F., 459
Schmidt, Lewis A., III, 639
Schmidt, Norman L., 15
Schreck, Kenneth M., 1
Schroeter, Marvin M., 199
Scott, H. William, Jr., 25
Sealy, Will C., 87
Seidenberg, Bernard, 743
Shedd, Donald P., 15
Shoemaker, William C., 105
Simon, Mildred Burtz, 56
Smith, Robert R., 427
Sonneland, John, 385
Speer, Francis D., 163
Speert, Harold, 245
Splithoff, C. A., 193
State, David, 545
Stearns, Maus W., Jr., 92
Steel, Howard H., 1
Stein, Irvin, 231
Stern, W. Eugene, 159

Taylor, Frederic W., 225
Thomas, Colin G., Jr., 137
Todd, Edwin M., Jr., 724
Trifon, Harry M., 495
Turner, M. Don, 511
Tyson, R. Robert, 1

Valk, William L., 82
Verney, E. B., 441
Vogler, William R., 586

Walker, James W., 511
Watson, T. A., 655
Waugh, John M., 145
Weber, Robert A., 199
Webster, J. E., 421
Weinberg, Sidney B., 687
Welch, J. W., 70
Werder, Alvar A., 605
Wheelock, Mark C., 489
Wilkins, Sam A., Jr., 586
Williams, William T., 435
Wright, William C., 1

Yesner, Raymond, 293

SUBJECT INDEX TO VOLUME 106

ABDOMEN, Abdominal injuries due to blunt force, ed. 355
Abnormalities and deformities, congenital, Unilateral cleft lip repair, 119; congenital, Failure of migration of rectal opening as cause for most cases of imperforate anus, 643; Technique employing hypothermia for repair of atrial septal defects, 751
Abscess, New approach to anorectal fistulous, based on high intermuscular lesion, 595
Accidents, automobile, Abdominal injuries due to blunt force, ed. 353
Adrenals, Clinical experiences with pheochromocytoma, 25; Thoracoabdominal incision for surgery of renal, and testicular neoplasms, 363
Aged, see Geriatrics
Ambulation, Survey on early, after surgery, 100
American College of Surgeons—Clinical Congress, Preliminary plans for 44th, The Conrad Hilton Hotel, Chicago, Illinois, October 6 to 10, 1958, 761
Ammonia, Etiology and treatment of, intoxication associated with disease of liver, 577
Anatomy, Surgical, of arterial supply to colon from superior mesenteric artery based upon study of 600 specimens, 385; Papilla of Vater and distal portions of common bile duct and duct of Wirsung, 687; Glandular structures of cervix uteri, 715
Anemia, Preoperative management of blood loss, 734
Aneurysm, aortic, Experiences with 165, homografts, 49; Surgical experiences in treatment of, of thoracic aorta, 179
Antibiotics, Bacteriologic and clinical experiences and methods of control of hospital infections due to, resistant staphylococci, 1; Efficacy of, combined with irrigation in experimental strangulated intestinal obstruction, 38; Comparison of complications following intestinal surgery after oral and parenteral preoperative, preparation, 145
Anus, Epidermoid carcinoma of anal region, 92; New approach to anorectal fistulous abscess based on high intermuscular lesion, 595; Lymphoid polyps (benign lymphoma) of rectum and, 639; Failure of migration of rectal opening as cause for most cases of imperforate, 643
Aorta, Experiences with 165, homografts, 49; Observations upon experimental repair of trachea using autogenous, and polyethylene tubes, 56; Effects of temporary ischemia on renal function under normal and hypothermic temperatures with aortic renal graft replacement, 82; Studies in extracorporeal circulation—IV, surgical techniques, 111; Surgical experiences in treatment of aneurysms of thoracic, 179; valves, Surgical treatment of, insufficiency by open plastic revision of tricuspid, to bicuspid, 679
Appendicitis, in older patient, 610
Arm, Arteriography of upper extremity, 63
Arrhythmia, Reoperation after resuscitation from cardiac arrest, 207
Arteries, Arteriography of upper extremity, 63; Effects of temporary ischemia on renal function under normal and hypothermic temperatures with aortic renal graft replacement, 82; Acute effects of complete heart block on pulmonary circulation, 333; Surgical anatomy of arterial supply to colon from superior mesenteric, based upon study of 600 specimens, 385; Peripheral arterial emboli, 399; Thrombo-endarterectomy of carotid bifurcation and internal carotid, 421; hepatic, Effects of afferent circulatory arrest upon hydrogen ion concentration of liver, 511; New needle and safer method of arteriography, 627; Experimental implantation of arterial homografts into ventricular myocardium, 709; Technique of anastomosing small, 743
Arteriography, New needle and safer method of, 627
Arthrodesis, Gill turnabout radial graft for wrist, 230
Asepsis, Ten year study on wound infections, 453
Atheroma, Thrombo-endarterectomy of carotid bifurcation and internal carotid artery, 421
Auscultation, as important aid to diagnosis of fractures, 713

BACTERIOPHAGE TYPING, Bacteriologic and clinical experiences and methods of control of hospital infections due to antibiotic resistant staphylococci, 1
Bile ducts, Postoperative cholangiography partially performed with patient in upright position, 242; Intraductal pressures and sphincteric resistance in canine pancreatic and biliary, after various stimuli, 306; Vitallium tube method for repair of strictures of, 409; Papilla of Vater and distal portions of common, and duct of Wirsung, 687
Biliary tract, Television radioscopy during operations on, passages, 747
Billroth II operation, New technique for gastrojejunostomy with, 238
Biology, Individual basis of biologic variability in cancer, ed. 227
Blood, Nature and treatment of postcommissurotomy hyponatremic syndrome, 87; circulation, Studies in extracorporeal,—IV, Surgical techniques, 111; coagulation, Critical evaluation of anticoagulant therapy in peripheral venous thrombosis and pulmonary embolism, 129; Two possible cases of acquired hypofibrinogenemia in newborn, 176; coagulation, Treatment of thromboembolism with aqueous heparin, 293; circulation, Acute effects of complete heart block on pulmonary, 333; loss, Continuous, automatic, electronic determinations of operative, 368; circulation, Thrombo-endarterectomy of carotid bifurcation and internal carotid artery, 421; volume, Indications for, determinations in major surgical procedures, 435; circulation, Effects of afferent circulatory arrest upon hydrogen ion concentration of liver, 511; Circulating lipids in experimental and human burns, 559; Etiology and treatment of ammonia intoxication associated with disease of liver, 577; circulation, Extracorporeal, in cardiac surgery, ed. 615; circulation, Surgical treatment of aortic insufficiency by open plastic revision of tricuspid aortic valve to bicuspid valve, 679; circulation, Study of effectiveness of "high pressure" cardiopneumonopexy in myocardial revascularization, 702; circulation, Experimental implantation of arterial homografts into ventricular myocardium, 709; loss, Technique for temporary control of bleeding during transesophageal suture ligation of esophageal varices, 749
Blood transfusion, Preoperative management of blood loss anemia, 734
Blood vessels, Respiratory and cardiovascular phenomena associated with pulmonary embolism, 271; Surgical anatomy of arterial supply to colon from superior mesenteric artery based upon study of 600 speci-

mens, 385; surgery, Study of 158 cases of esophageal varices, 519
Bone, Tumors, of scapula and clavicle, 536
Brain, blood supply, Thrombo-endarterectomy of carotid bifurcation and internal carotid artery, 421; Studies of cerebrospinal fluid pressure during hypothermia in intracranial surgery, 555
Breast, Intracystic carcinoma of, 347; Analysis of 2,514 examinations during early phases of x-ray survey of, 478
Burns, Circulating lipids in experimental and human, 559

CANCER, Survey of tongue, over 15 year period in general hospital, 15; Epidermoid carcinoma of anal region, 92; Use of l-triiodothyronine as pituitary depressant in management of thyroid, 137; Sinus histiocytosis of lymph nodes in, 163; Nuts, eggs, and, ed. 225; Individual basis of biologic variability in, ed. 227; Carcinoma of colon and rectum, 257; Rationale of subtotal and total colectomy in treatment of, and multiple polyps of colon, 288; Intracystic carcinoma of breast, 347; controversy, ed. 353; Prevention of experimental lung metastases with triethylenethiophosphoramide (THIOTEPA), 427; Experience with triethylene melamine (TEM) and triethylene thiophosphoramide (THIOTEPA) in recurrent or metastatic solid tumors, 459; Technique for, isolation and extended dissection for, of distal colon and rectum, 466; Analysis of 2,514 examinations during early phases of x-ray survey of breast, 478; Immediate frozen section diagnosis, 489; Detection and localization of preclinical carcinoma of cervix by contact smears, 495; Clinical evaluation of malignant melanoma, 586; metastasis, Effect upon hypophysis of radioactive yttrium, 600; Multicentric carcinomas of oral cavity, 652; Lesions of salivary glands, 655; Five year survival after anterior resection for carcinoma of rectum and rectosigmoid, 695
Carcinoma, see Cancer
Cardiac arrest, see Arrhythmia
Cardiopneumonopexy, Study of effectiveness of "high pressure", in myocardial revascularization, 702
Cells, cancer, dissemination, Technique for, isolation and extended dissection for, of distal colon and rectum, 466
Cerebrospinal fluid, Studies of, pressure during hypothermia in intracranial surgery, 555
Certification, Can, be separated from graduate education in surgery, ed. 97
Cesarean hysterectomy, Edoardo Porro and, 245
Children, Meckel's diverticulum in childhood, 11; Roentgenographic study of lumbrosacral spine in, 193; Pulmonary resection for tuberculosis in, 196
Cirrhosis, Sources of upper gastrointestinal bleeding in patients with, 153; Study of 158 cases of esophageal varices, 519; Natural history of patient with, of liver with esophageal varices following first massive hemorrhage, 699
Clavicle, Tumors of scapula and, 536
Clostridium welchii, Comparison of in vivo changes following administration of strangulation obstruction fluid and, toxin, 667
Colon, Carcinoma of, and rectum, 257; Rationale of subtotal and total colectomy in treatment of cancer and multiple polyps of, 288; secretion, Effects of, of stomach, duodenum, jejunum, and, on esophagus of dog, 337; Surgical anatomy of arterial supply to, form superior mesenteric artery based upon study of 600 specimens, 385; Technique for cancer isolation and extended dissection for cancer of distal, and rectum, 466
Contrast media, Role of water soluble, in gastrointestinal tract obstruction, 567
Cytology, Detection and localization of preclinical carcinoma of cervix by contact smears, 495

DIAGNOSIS, Individual basis of biologic variability in cancer, ed. 227; Surgical, and management of dysfunctional uterine bleeding, 321; Cancer controversy, ed. 353; Operative aspects of Richter's hernia, 358; Analysis of 2,514 examinations during early phases of x-ray survey of breast, 478; Immediate frozen section, 489; Detection and localization of preclinical carcinoma of cervix by contact smears, 495
Diarrhea, Fifth column at battle of Gettysburg, 375
Diuresis, Some aspects of water and electrolyte excretion, 441
Duct of Wirsung, see Pancreatic ducts
Duodenum, Hiatus hernia, peptic esophagitis, and peptic ulcer, 77; secretion, Effects of, of stomach, jejunum, and colon on esophagus of dog, 337
Dura mater, Surgical application of freeze-dried homologous, 159
Dysentery, Fifth column at battle of Gettysburg, 375

EDEMA, pulmonary, Acute effects of complete heart block on, circulation, 333
Education, surgical, Can certification be separated from graduate education in surgery, ed. 97; surgical, Specialization versus generalization, dilemma of surgical training, ed. 739; surgical, Behold, torch, ed. 741
Electrolytes, balance, Use of serum freezing point depressions in evaluating salt and water, in preoperative and postoperative states, 41; Some aspects of water and, excretion, 441
Embolism, pulmonary, Critical evaluation of anticoagulant therapy in peripheral venous thrombosis and, 129; pulmonary, Respiratory and cardiovascular phenomena associated with, 271; Treatment of thromboembolism with aqueous heparin, 293; Peripheral arterial emboli, 399
Embryology, Failure of migration of rectal opening as cause for most cases of imperforate anus, 643
Endometrium, of normal postmenopausal women, 413
Esophagus, Hiatus hernia, peptic esophagitis, and peptic ulcer, 77; Effects of secretions of stomach, duodenum, jejunum, and colon on, of dog, 337; Study of 158 cases of esophageal varices, 519; Transabdominal repair of hiatal hernia, 549; varices, Natural history of patient with cirrhosis of liver with, following first massive hemorrhage, 699; Technique for temporary control of bleeding during transesophageal suture ligation of esophageal varices, 749
Extremities, Arteriography of upper, 63

FINGER, Treatment of mallet, by complete metacarpophalangeal flexion, 233
Fistula, New approach to anorectal fistulous abscess based on high intermuscular lesion, 595
Fluid, Efficacy of antibiotics combined with irrigation in experimental strangulated intestinal obstruction, 38; Comparison of in vivo changes following administration of strangulation obstruction, and Clostridium welchii toxin, 667
Foot, Tarsometatarsal fracture dislocations, 623
Fractures, General principles of, management in aged, 343; Tarsometatarsal, dislocations, 623; Auscultation as important aid to diagnosis of, 713
Freezing, Surgical application of, homologous dura mater, 159

GALLBLADDER, Postoperative cholangiography partially performed with patient in upright position, 242
Gamma globulin, Effect of skin transplants on serum proteins in experimental animals, 605

Gastrectoplasty, New approach to surgical management of peptic ulcer by, 105
Gastric acid, Inhibitory role of pyloric antrum on cephalic phase of, secretion in dogs, 545
Gastrointestinal tract, Sources of upper, bleeding in patients with cirrhosis, 153; Role of water soluble contrast media in, obstruction, 567; Etiology and treatment of ammonia intoxication associated with disease of liver, 577
Gastrostomy, tubes, 631
Generalization, Specialization versus, dilemma of surgical training, ed. 739
Geriatrics, General principles of fracture management in aged, 343; Appendicitis in older patient, 610
Gettysburg, Fifth column at battle of, 375
Gill, turnabout radial graft for wrist arthrodesis, 230
Glands, Glandular structures of cervix uteri, 715
Grafts, Experiences with 165 aortic homografts, 49; Observations upon experimental repair of trachea using autogenous aorta and polyethylene tubes, 56; Effects of temporary ischemia on renal function under normal and hypothermic temperatures with aortic renal, replacement, 82; Surgical application of freeze-dried homologous dura mater, 159; Surgical experiences in treatment of aneurysms of thoracic aorta, 179; Gill turnabout radial, for wrist arthrodesis, 230; Effect of skin transplants on serum proteins in experimental animals, 605; Pattern of wound healing of skin autografts and skin homografts in rat, 671; Study of effectiveness of "high pressure" cardiopneumonopexy in myocardial revascularization, 702; Experimental implantation of arterial homografts into ventricular myocardium, 709

HEART, Nature and treatment of postcommissurotomy hyponatremic syndrome, 87; Studies in extracorporeal circulation—IV, surgical techniques, 111; Critical evaluation of anticoagulant therapy in peripheral venous thrombosis and pulmonary embolism, 129; Reoperation after resuscitation from cardiac arrest, 207; Respiratory and cardiovascular phenomena associated with pulmonary embolism, 271; block, Acute effects of complete, on pulmonary circulation, 333; Extracorporeal circulation in cardiac surgery, ed. 615; Surgical treatment of aortic insufficiency by open plastic revision of tricuspid aortic valve to bicuspid valve, 679; Study of effectiveness of "high pressure" cardiopneumonopexy in myocardial revascularization, 702; Experimental implantation of arterial homografts into ventricular myocardium, 709; Technique employing hypothermia for repair of atrial septal defects, 751
Hemoglobin, Comparison of hematologic responses following routine prenatal administration of intramuscular and oral iron, 516
Hemorrhage, Sources of upper gastrointestinal bleeding in patients with cirrhosis, 153; Management of bleeding peptic ulcer, 199; Surgical diagnosis and management of dysfunctional uterine bleeding, 321; Prevention of massive, secondary to hemorrhoidectomy, 485; Effects of afferent circulatory arrest upon hydrogen ion concentration of liver, 511; Natural history of patient with cirrhosis of liver with esophageal varices following first massive, 699
Hemorrhoids, Prevention of massive hemorrhage secondary to hemorrhoidectomy, 485
Heparin, Treatment of thromboembolism with aqueous, 293
Hernia, Hiatus, peptic esophagitis, and peptic ulcer, 77; Operative aspects of Richter's, 358; Transabdominal repair of hiatal, 549
Histiocytosis, Sinus, of lymph nodes in cancer, 163
Hormones, Use of l-triiodothyronine as pituitary depressant in management of thyroid cancer, 137
Hospital, Bacteriologic and clinical experiences and methods of control of, infections due to antibiotic resistant staphylococci, 1
Hydrogen ion concentration, Effects of afferent circulatory arrest upon, of liver, 511
Hypaque sodium, Role of water soluble contrast media in gastrointestinal tract obstruction, 567
Hypofibrinogenemia, Two possible cases of acquired, in newborn, 176
Hypophysis, Effect upon, of radioactive yttrium, 600
Hypothermia, Collapsible tub for immersion cooling on operating table, 502; Studies of cerebrospinal fluid pressure during, in intracranial surgery, 555; Technique employing, for repair of atrial septal defects, 751
Hysterectomy, cesarean, Edoardo Porro and, 245; Surgical complications of vaginal, 527

INCISION, Thoracoabdominal, for surgery of renal, adrenal, and testicular neoplasms, 363
Infants, newborn, Two possible cases of acquired hypofibrinogenemia in, 176
Infection, Bacteriologic and clinical experiences and methods of control of hospital, due to antibiotic resistant staphylococci, 1; Ten year study on wound, 453
Injuries, Abdominal, due to blunt force, ed. 353
Instruments and apparatus, for collection of blood, venous cannula, Studies in extracorporeal circulation—IV, surgical techniques, 111; Postoperative cholangiography partially performed with patient in upright position, 242; photokymograph, Intraductal pressures and sphincteric resistance in canine pancreatic and biliary ducts after various stimuli, 306; automatic blood loss meter, Continuous, electronic determinations of operative, 368; setup for contact smears, Detection and localization of preclinical carcinoma of cervix by, 495; Collapsible tub for immersion cooling on operating table, 502; New needle and safer method of arteriography, 627; Television radioscopy during operations on biliary passages, 747
Intestines, Meckel's diverticulum in childhood, 11; Efficacy of antibiotics combined with irrigation in experimental strangulated intestinal obstruction, 38; Comparison of complications following intestinal surgery after oral and parenteral preoperative antibiotic preparation, 145; Operative aspects of Richter's hernia, 358; Comparison of in vivo changes following administration of strangulation obstruction fluid and Clostridium welchii toxin, 667
Iron, Comparison of hematologic responses following routine prenatal administration of intramuscular and oral, 516; deficiency, Preoperative management of blood loss anemia, 734
Irrigation, peritoneal, Efficacy of antibiotics combined with, in experimental strangulated intestinal obstruction, 38
Ischemia, Effects of temporary, on renal function under normal and hypothermic temperatures with aortic renal graft replacement, 82

IEJUNUM, New technique for gastrojejunostomy with Billroth II operation, 238; secretion, Effects of, of stomach, duodenum, and colon on esophagus of dog, 337

KIDNEY, Effects of temporary ischemia on renal function under normal and hypothermic temperatures with aortic renal graft replacement, 82; Thoracoabdominal incision for surgery of renal, adrenal, and testicular neoplasms, 363; function, Some aspects of water and electrolyte excretion, 441

L-Triiodothyronine, Use of, as pituitary depressant in management of thyroid cancer, 137
Lamina, Simple excision of unattached, for spondylolysis, 724
Leucocytes, Comparison of in vivo changes following administration of strangulation obstruction fluid and Clostridium welchii toxin, 667
Lip, Unilateral cleft, repair, 119
Lipids, Circulating, in experimental and human burns, 559
Liver, Sources of upper gastrointestinal bleeding in patients with cirrhosis, 153; Effects of afferent circulatory arrest upon hydrogen ion concentration of, 511; Study of 158 cases of esophageal varices, 519; Etiology and treatment of ammonia intoxication associated with disease of, 577; Natural history of patient with cirrhosis of, with esophageal varices following first massive hemorrhage, 699
Lungs, Critical evaluation of anticoagulant therapy in peripheral venous thrombosis and pulmonary embolism, 129; Pulmonary resection for tuberculosis in children, 196; Respiratory and cardiovascular phenomena associated with pulmonary embolism, 271; blood supply, Acute effects of complete heart block on pulmonary circulation, 333; Prevention of experimental, metastases with triethylenethiophosphoramide (Thiotepa), 427; Extracorporeal circulation in cardiac surgery, ed. 615; Study of effectiveness of "high pressure" cardiopneumonopexy in myocardial revascularization, 702
Lymph, Circulating lipids in experimental and human burns, 559; follicles, in cervix uteri, 729
Lymph nodes, Sinus histiocytosis of, in cancer, 163; dissection, Clinical evaluation of malignant melanoma, 586
Lymphoma, Malignant, of thyroid, 70; Lymphoid polyps (benign,) of rectum and anus, 639

Meckel's diverticulum, in childhood, 11
Melanoma, Clinical evaluation of malignant, 586
Menopause, Endometria of normal postmenopausal women, 413
Metabolism, Circulating lipids in experimental and human burns, 559
Metacarpophalangeal joints, Treatment of mallet finger by complete, flexion, 233
Metatarsus, Tarsometatarsal fracture dislocations, 623
Mitral valve, Nature and treatment of postcommissurotomy hyponatremic syndrome, 87
Mouth, Multicentric carcinomas of oral cavity, 652
Mucous membrane, Multicentric carcinomas of oral cavity, 652
Muscles, New approach to anorectal fistulous abscess based on high intermuscular lesion, 595
Myocardium, Study of effectiveness of "high pressure" cardiopneumonopexy in myocardial revascularization, 702; Experimental implantation of arterial homografts into ventricular, 709

Needle, New, and safer method of arteriography, 627
Nose, Selection of patients for rhinoplasty, ed. 481

Old age, see Geriatrics
Oral cavity, Multicentric carcinomas of, 652
Osmosis, Some aspects of water and electrolyte excretion, 441
Oxygenator, Extracorporeal circulation in cardiac surgery, ed. 615

Pancreatic ducts, Intraductal pressures and sphincteric resistance in canine, and biliary, after various stimuli, 306; Papilla of Vater and distal portions of common bile, and duct of Wirsung, 687
Pancreatography, Papilla of Vater and distal portions of common bile duct and duct of Wirsung, 687
Papilla of Vater, and distal portions of common bile duct and duct of Wirsung, 687
Parotid gland, Parotidectomy for chronic or recurrent sialadenitis, 573; Lesions of salivary glands, 655
Pathology, Immediate frozen section diagnosis, 489
Pectus excavatum, Operation for correction of, 618
Penicillin, Comparison of in vivo changes following administration of strangulation obstruction fluid and Clostridium welchii toxin, 667
Peptic ulcer, Hiatus hernia, peptic esophagitis, and, 77; New approach to surgical management of, by gastrectoplasty, 105; Management of bleeding, 199; Inhibitory role of pyloric antrum on cephalic phase of gastric acid secretion in dogs, 545
Pheochromocytoma, Clinical experiences with, 25
Phosphorus, radioactive, Circulating lipids in experimental and human burns, 559
Physiology, Intraductal pressures and sphincteric resistance in canine pancreatic and biliary ducts after various stimuli, 306
Pituitary body, depressant, Use of l-triiodothyronine as, in management of thyroid cancer, 137; Effect upon hypophysis of radioactive yttrium, 600
Polyethylene, Observations upon experimental repair of trachea using autogenous aorta and, tubes, 56
Polyps, Lymphoid, (benign lymphoma) of rectum and anus, 639
Porro, Edoardo, and cesarean hysterectomy, 245
Portal vein, Effects of afferent circulatory arrest upon hydrogen ion concentration of liver, 511; Study of 158 cases of esophageal varices, 519
Pregnancy, Comparison of hematologic responses following routine prenatal administration of intramuscular and oral iron, 516
Proteins, Effect of skin transplants on serum, in experimental animals, 605
Pylorus, Inhibitory role of pyloric antrum on cephalic phase of gastric acid secretion in dogs, 545

Radioactivity, Circulating lipids in experimental and human burns, 559; Effect upon hypophysis of radioactive yttrium, 600
Radioscopy, Television, during operations on biliary passages, 747
Radius, Gill turnabout radial graft for wrist arthrodesis, 230
Rectum, Carcinoma of colon and, 257; Technique for cancer isolation and extended dissection for cancer of distal colon and, 466; New approach to anorectal fistulous abscess based on high intermuscular lesion, 595; Lymphoid polyps (benign lymphoma) of, and anus, 639; Failure of migration of rectal opening as cause for most cases of imperforate anus, 643; Five year survival after anterior resection for carcinoma of, and rectosigmoid, 695
Resuscitation, Reoperation after, from cardiac arrest, 207
Rhinoplasty, Selection of patients for, ed. 481
Roentgenography, Arteriography of upper extremity, 63; Roentgenographic study of lumbosacral spine in children, 193; Postoperative cholangiography partially performed with patient in upright position, 242; Analysis of 2,514 examinations during early phases of x-ray survey of breast, 478; Role of water soluble contrast media in gastrointestinal tract obstruction, 567

Salivary gland, Parotidectomy for chronic or recurrent sialadenitis, 573; Lesions of, 655
Sarcoma, Malignant lymphoma of thyroid, 70; Tumors of scapula and clavicle, 536

Scapula, Tumors of, and clavicle, 536
Serum, Use of, freezing point depressions in evaluating salt and water balance in preoperative and postoperative states, 41; Effect of skin transplants on, proteins in experimental animals, 605
Sigmoid, Five year survival after anterior resection for carcinoma of rectum and rectosigmoid, 695
Skin, graft, Effect of, transplants on serum proteins in experimental animals, 605; graft, Pattern of wound healing of, autografts and, homografts in rat, 671
Smears, Detection and localization of preclinical carcinoma of cervix by contact, 495
Sodium, chloride, Use of serum freezing point depressions in evaluating salt and water balance in preoperative and postoperative states, 41
Specialization, Can certification be separated from graduate education in surgery, ed. 97; versus generalization, the dilemma of surgical training, ed. 739
Spine, Roentgenographic study of lumbosacral, in children, 193; Simple excision of unattached lamina for spondylolysis, 724
Spondylolysis, Simple excision of unattached lamina for, 724
Staphylococcus, Bacteriologic and clinical experiences and methods of control of hospital infections due to antibiotic resistant, 1; Ten year study on wound infections, 453
Stomach, Hiatus hernia, peptic esophagitis, and peptic ulcer, 77; New approach to surgical management of peptic ulcer by gastrectoplasty, 105; New technique for gastrojejunostomy with Billroth II operation, 238; secretion, Effects of, of, duodenum, jejunum, and colon on esophagus of dog, 337; secretion, Inhibitory role of pyloric antrum on cephalic phase of gastric acid, in dogs, 545; Gastrostomy tubes, 631
Sublingual gland, Lesions of salivary glands, 655
Submaxillary gland, Lesions of salivary glands, 655
Surgeon, "Unique", ed. 484; Behold, torch, ed. 741
Surgery, preoperative and postoperative care, Use of serum freezing point depressions in evaluating salt and water balance in, states, 41; plastic, Experiences with 165 aortic homografts, 49; plastic, Observations upon experimental repair of trachea using autogenous aorta and polyethylene tubes, 56; postoperative complications, Nature and treatment of postcommissurotomy hyponatremic syndrome, 87; Can certification be separated from graduate education in, ed. 97; postoperative care, Survey on early ambulation after, 100; technique, New approach to surgical management of peptic ulcer by gastrectoplasty, 105; technique, Studies in extracorporeal circulation—IV, surgical, 111; plastic, Unilateral cleft lip repair, 119; postoperative, Comparison of complications following intestinal, after oral and parenteral preoperative antibiotic preparation, 145; Surgical application of freeze-dried homologous dura mater, 159; Surgical experiences in treatment of aneurysms of thoracic aorta, 179; Pulmonary resection for tuberculosis in children, 196; Management of bleeding peptic ulcer, 199; Reoperation after resuscitation from cardiac arrest, 207; Experimental and clinical evaluation of surgical suture materials—III, 216; technique, New, for gastrojejunostomy with Billroth II operation, 238; mortality, Carcinoma of colon and rectum, 257; colectomy, Rationale of subtotal and total, in treatment of cancer and multiple polyps of colon, 288; Surgical diagnosis and management of dysfunctional uterine bleeding, 321; experimental, Effects of secretions of stomach, duodenum, jejunum, and colon on esophagus of dog, 337; Cancer controversy, ed. 353; technique, Operative aspects of Richter's hernia, 358; Continuous, automatic, electronic determinations of operative blood loss, 368; Peripheral arterial emboli, 399; technique, Vitallium tube method for repair of strictures of bile ducts, 409; technique, Thromboendarterectomy of carotid bifurcation and internal carotid artery, 421; postoperative care, Indications for blood volume determinations in major surgical procedures, 435; postoperative complications, Ten year study on wound infections, 453; Technique, for cancer isolation and extended dissection for cancer of distal colon and rectum, 466; plastic, Selection of patients for rhinoplasty, ed. 481; progress, "Unique" surgeon, ed. 484; technique, Prevention of massive hemorrhage secondary to hemorrhoidectomy, 485; aids in, Immediate frozen section diagnosis, 489; Surgical complications of vaginal hysterectomy, 527; Transabdominal repair of hiatal hernia, 549; Studies of cerebrospinal fluid pressure during hypothermia in intracranial, 555; principles and surgical practice, Fetishism in, ed. 613; Extracorporeal circulation in cardiac, ed. 615; Operation for correction of pectus excavatum, 618; postoperative care, Gastrostomy tubes, 631; plastic, Pattern of wound healing of skin autografts and skin homografts in rat, 671; technique, Surgical treatment of aortic insufficiency by open plastic revision of tricuspid aortic valve to bicuspid valve, 679; Five year survival after anterior resection for carcinoma of rectum and rectosigmoid, 695; Simple excision of unattached lamina for spondylolysis, 724; Preoperative management of blood loss anemia, 734; Specialization versus generalization, dilemma of surgical training, ed. 739; Technique, of anastomosing small arteries, 743; Television radioscopy during operations on biliary passages, 747; Technique, for temporary control of bleeding during transesophageal suture ligation of esophageal varices, 749; Technique, employing hypothermia for repair of atrial septal defects, 751
Suture, materials, plain catgut, chromicized catgut, braided perlon wound, healing, Experimental and clinical evaluation of surgical, III, 216

Television, radioscopy during operations on biliary passages, 747
Temperature, Effects of temporary ischemia on renal function under normal and hypothermic, with aortic renal graft replacement, 82; Collapsible tub for immersion cooling on operating table, 502
Tendon, surgery, Treatment of mallet finger by complete metacarpophalangeal flexion, 233
Terminology, Nuts, eggs, and cancer, ed. 225
Testis, Thoracoabdominal incision for surgery of renal, adrenal, and testicular neoplasms, 363
Thorax, Operation for correction of pectus excavatum, 618
Thrombosis, Critical evaluation of anticoagulant therapy in peripheral venous, and pulmonary embolism, 129; Treatment of thromboembolism with aqueous heparin, 293; Peripheral arterial emboli, 399; Thromboendarterectomy of carotid bifurcation and internal carotid artery, 421
Thyroid, Malignant lymphoma of, 70; Use of l-triiodothyronine as pituitary depressant in management of, cancer, 137
Tissue, sections, Immediate frozen, diagnosis, 489
Tongue, Survey of, cancer over 15 year period in general hospital, 15
Trachea, Observations upon experimental repair of, using autogenous aorta and polyethylene tubes, 56
Triethylene melamine (TEM), Experience with, and triethylene thiophosphoramide (Thiotepa) in recurrent or metastatic solid tumors, 459
Triethylenethiophosphoramide (Thiotepa), Prevention of experimental lung metastases with, 427; Experience with triethylene melamine (TEM) and, in recurrent or metastatic solid tumors, 459

Tub, Collapsible, for immersion cooling on operating table 502
Tuberculosis, Pulmonary resection for, in children, 196
Tubes, Gastrostomy, 631
Tumors, Clinical experiences with pheochromocytoma, 25; polyps, multiple, Rationale of subtotal and total colectomy in treatment of cancer and, of colon, 288; Intracystic carcinoma of breast, 347; Thoracoabdominal incision for surgery of renal, adrenal, and testicular neoplasms, 363; Experience with triethylene melamine (TEM) and triethylene thiophosphoramide (THIOTEPA) in recurrent or metastatic solid, 459; of scapula and clavicle, 536; Lesions of salivary glands, 655

UTERUS, Edoardo Porro and cesarean hysterectomy, 245; Surgical diagnosis and management of dysfunctional uterine bleeding, 321; Endometria of normal postmenopausal women, 413; Surgical complications of vaginal hysterectomy, 527
Uterus cervix, Detection and localization of preclinical carcinoma of, by contact smears, 495; Glandular structures of, 715; Lymph follicles in, 729

VALVES, Surgical treatment of aortic insufficiency by open plastic revision of tricuspid aortic, to bicuspid, 679
Varices, Study of 158 cases of esophageal, 519; Technique for temporary control of bleeding during transesophageal suture ligation of esophageal, 749
Veins, Critical evaluation of anticoagulant therapy in peripheral venous thrombosis and pulmonary embolism, 129
Vitallium, tube method for repair of strictures of bile ducts, 409

WATER, balance, Use of serum freezing point depressions in evaluating salt and, in preoperative and postoperative states, 41; Some aspects of, and electrolyte excretion, 441
Wounds, Ten year study on, infections, 453; Circulating lipids in experimental and human burns, 559; healing, Pattern of, of skin autografts and skin homografts in rat, 671
Wrist, Gill turnabout radial graft for, arthrodesis, 230

YTTRIUM, Effect upon hyophysis of radioactive, 600

INDEX TO BOOK REVIEWS

ALAJOUANINE, PR. TH. La douleur et les douleurs, with 22 collaborators, 506

AMERICAN CANCER SOCIETY, INC., and NATIONAL CANCER INSTITUTE U. S. PUBLIC HEALTH SERVICE; Proceedings of the Third National Cancer Conference, Detroit, Michigan, June 4-6, 1956, 252

ARCHER, W. HARRY. A Manual of Oral Surgery; a Step-by-Step Atlas of Operative techniques, 2nd ed., 636

ATLAS OF TUMOR PATHOLOGY. Section III, Fascicle 7—Tumors of the Cardiovascular System by Benjamin H. Landing and Sidney Farber. Section V, Fascicle 19—Tumors of the Thymus Gland by Benjamin Castleman, 507

ATLEE, H. B. The Gist of Obstetrics. Illustrated by Garth Vaughan, 254

BARROW, DAVID WOOLFOLK. The Clinical Management of Varicose Veins, with a foreword by Arthur W. Allen. 2nd rev. enl. ed., 255

BEIERWALTES, WILLIAM H., JOHNSON, PHILIP C., and SOLARI, ARTHUR J. Clinical Use of Radioisotopes, 125

BÖHLER, LORENZ. The Treatment of Fractures, Vol. 2, 123

BROCHER, J. E. W. Die Prognose der Wirbelsäulenleiden; eine berufsprophylaktische Betrachtung, 380

CECIL, RUSSELL L. The Specialities in General Practice, edited by Russell L. Cecil and Howard F. Conn, 2nd ed., 508

CHARNY, CHARLES W., and WOLGIN, WILLIAM. Cryptorchism, 505

CROWE, SAMUEL JAMES. Halsted of Johns Hopkins; the Man and his Men, 379

DAHLIN, DAVID C. Bone Tumors; General Aspects and an Analysis of 2,276 Cases, 254

DEBRUNNER, HANS. Die Therapie des angeborenen Klumpfusses, 634

DOUGLAS, R. GORDON, and STROMME, WILLIAM B. Operative Obstetrics, with foreword by Nicholson J. Eastman, 758

DREYFUS, CAMILLE. Some Milestones in the History of Hematology, with foreword by Sir Lionel E. H. Whitby, 760

EVANS, F. GAYNOR. Stress and Strain in Bones; their Relation to Fractures and Osteogenesis, 636

FASANELLA, R. M. Management of Complications in Eye Surgery; Avoidance of Pitfalls and Treatment of Difficult Situations in Ophthalmologic Operations, edited by R. M. Fasanella, 758

FISHBEIN, MORRIS. 1957 Medical Progress; a Review of Medical Advances During 1956, edited by Morris Fishbein, 126

FOLDES, FRANCIS F. Muscle Relaxants in Anesthesiology, illustrated by Margaret M. Croup, 506

FORESTIER, J., JACQUELINE, F., and ROTES-QUEROI, J. Ankylosing Spondylitis; Clinical Considerations, Roentgenology, Pathologic Anatomy, Treatment, translated by A. U. Desjardins, 253

FURLONG, RONALD. Injuries of the Hand, 381

GILLIES, SIR HAROLD, and MILLARD, RALPH, JR. The Principles and Art of Plastic Surgery. Chapter on Anaesthesia by Ivan Magill, with foreword by Jerome Pierce Webster, Vols. 1 and 2, 125

GUILLAUME, J., BILLET, R., CARON, J. P., and CUCCIA, D. Les méningiomes; étude clinique et chirurgicale, 251

GUILLAUME, J., MAZARS, G., ROGÉ, R., and PANSINI, A. Les accidents circulatoires du cerveau; traitement chirurgical de l'hémorragie et de l'ischémie, 251

HENRY, ARNOLD K. Extensile Exposure, second edition, 757

ILLINGWORTH, CHARLES F. W., and DICK, BRUCE M. A Text-book of Surgical Pathology, 7th ed., 637

INTERNATIONAL CONGRESS OF GASTROENTEROLOGY. Fifth meeting of l'Association des Sociétés Européennes et Méditerranéennes de Gastro-Entérologie, London, July 18-21, 1956, 756

LANGSTON, HIRAM T., PANTONE, ANTON M., and MELAMED, MYRON. The Postoperative Chest; Radiographic Considerations After Thoracic Surgery, 759

LEGER, LUCIEN, and BREHANT, JACQUES. Chirurgie du pancreas, 756

LEOPOLD, SIMON S. The Principles and Methods of Physical Diagnosis; Correlation of Physical Signs with Certain Physiological and Pathological Changes in Disease; with a chapter on Sounds from the Thorax; Acoustic Principles by S. Reid Warren, Jr., 2nd ed., 508

LITTLE, DAVID M., JR. "Controlled Hypotension" in Anesthesia and Surgery, 127

LOVEJOY, ESTHER POHL. Women Doctors of the World, 379

MAINGOT, RODNEY. The Management of Abdominal Operations, edited by Rodney Maingot, 2nd ed., vols. 1 and 2, 634

MARSHALL, VICTOR F. Textbook of Urology, 637

MARTIN, HAYES. Surgery of Head and Neck Tumors, 636

MAYO CLINIC. Collected Papers of the Mayo Clinic and the Mayo Foundation, edited by Richard M. Hewitt, vol. 48, 1956, 251

MEAKINS, JONATHAN CAMPBELL. The Practice of Medicine, edited by Jonathan Campbell Meakins, 6th ed., 126

MILHIET, HENRI, and JAGER, PAUL. Anatomie et chirurgie du péricarde; applications à la chirurgie broncho-pulmonaire, preface by J. Baumann, 252

MOBIUS, W., and HILMERTH, HARALD. Der hohe Gradstand, 127

MOORE, SHERWOOD. Hyperostosis Cranii. Stewart-Morel Syndrome; Metabolic Craniopathy Morgagni's Syndrome; Stewart-Morel-Moore Syndrome (Ritvo); Le Syndrome de Morgagni-Morel, 125

NACLERIO, EMIL A. Bronchopulmonary Diseases; Basic Aspects, Diagnosis and Treatment, edited by Emil A. Naclerio, 756

NADAS, ALEXANDER S. Pediatric Cardiology, 124

NAUJOKS, H. Gerichtliche Geburtshilfe, 251

OUGHTERSON, ASHLEY W. Medical Effects of the Atomic Bomb in Japan, edited by Ashley W. Oughterson and Shields Warren, 506

PAP, K. Die Diafixation ein Verfahren zur versorgung schwer Einrichtbarer und zu Verschiebung neigender Schaftbrueche, 759

PUESTOW, CHARLES B. Surgery of the Biliary Tract, Pancreas and Spleen; a Handbook of Operative Surgery, illustrated by Jessie W. Phillips, 2nd ed., 509

QUEEN CHARLOTTE HOSPITAL. The Queen Charlotte's Text-Book of Obstetrics, edited by S. G. Clayton, 9th ed., 637

QUICK, ARMAND J. Hemorrhagic Diseases, 127

ROB, CHARLES. Operative Surgery. Vol. 3—Rectum and Anus; Thorax. Vol. 4—Head and Neck and Clearance of Lymph Nodes, Vascular Surgery, Endocrine Glands. Edited by Charles Rob and Rodney Smith, 382

ROBERTSON, E. GRAEME. Pneumoencephalography, 757

SCAGLIETTI, O. Archivio "Putti" di Chirurgia Degli Organi di Movimento, vol. 7, 124

SERFLING, HANS JOACHIM. Die Hypospadie und ihre Behandlung, 379

SNIVELY, WILLIAM D., JR., and SWEENEY, MICHAEL J. Fluid Balance Handbook for Practitioners, illustrated by Kathleen Calhoun, 254

SURGERY IN WORLD WAR II. Orthopedic Surgery in the Mediterranean Theater of Operations, by Oscar P. Hampton, Jr, edited by John B. Coates, Jr., Mather Cleveland, and E. M. McFetridge, 507, 760

THEOBALD, G. W. The Pregnancy Toxemias or the Encymonic Atelositeses, with a chapter on the Adrenal Cortex by John Dawson, 252

THORWALD, JÜRGEN. The Century of the Surgeon, 635

TRANSACTIONS of the INTERNATIONAL SOCIETY of PLASTIC SURGEONS. First Congress (Stockholm and Uppsala 1955), edited by Tord Skoog, 759

YOUMANS, W. B. Fundamentals of Human Physiology for Students in the Medical Sciences, 127

ZIMMERMAN, LEO M., and LEVINE, RACHMIEL. Physiologic Principles of Surgery, 255

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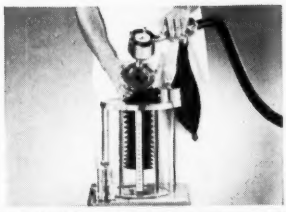
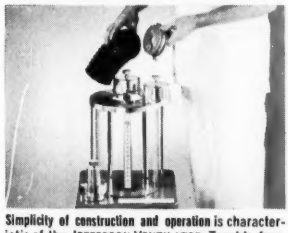


Vertical scale shows delivered volume, and convenient chart on platform gives corrections for gas flow at various rates of respiration (essential for accuracy with any bellows-type volume indicator).



Simplicity of construction and operation is characteristic of the JEFFERSON VENTILATOR. Trouble-free, automatic overflow valve in collar casting prevents overfilling bellows during high gas flows.

New, optional NRB Head, for use with any model JEFFERSON VENTILATOR, for the first time makes possible mechanical ventilation with intermittent negative and positive pressures during non-rebreathing anesthesia techniques.

THE JEFFERSON VENTILATOR is a clinically proved, auto-pneumatic, portable device to help insure proper pulmonary ventilation during general anesthesia in every type of patient, and especially in the poor-risk patient or during open-chest surgery. Separate controls for phase, rate, negative and positive pressures maintain optimal mean airway pressure. Simply designed and easily regulated, the JEFFERSON VENTILATOR is now used routinely in the teaching hospitals of more than three-quarters of medical schools throughout the United States.

AUTOMATICALLY delivering properly phased negative and positive pressures through the endotracheal tube, the JEFFERSON VENTILATOR helps prevent respiratory acidosis, does not embarrass circulation, frees both hands of the anesthesiologist. However, manual control of rebreathing bag may be quickly resorted to if desired. Finally, negative and positive pressures, rate and phase of the JEFFERSON VENTILATOR may be adjusted *separately* to changing requirements. *For orders or information, phone collect:* OSborne 5-5200, AIR-SHIELDS, INC., Hatboro, Pa.

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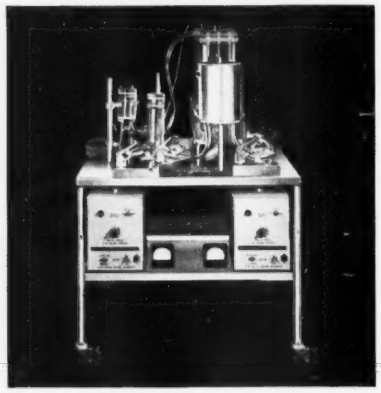
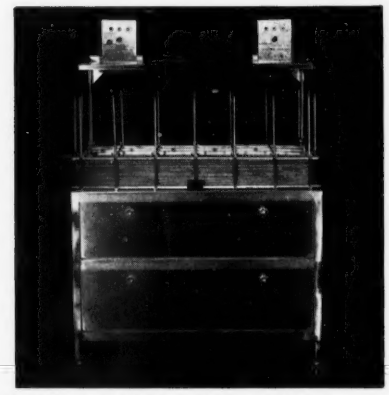
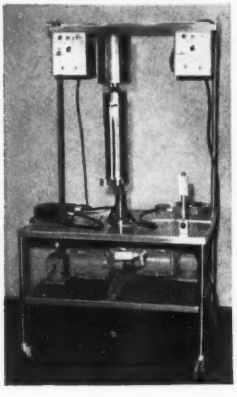
MARK first to offer a complete line of instruments for maintenance of Cardiorespiratory Functions During Cardiac Bypass



MARK II HEART-LUNG The screen type oxygenator of the apparatus is extremely simple in design, consisting of stainless steel fine mesh screens that increase oxygenating efficiency without damage to the blood. The screens are suspended in a plastic distributing chamber and blood is gently filmed on them in an atmosphere of oxygen . . . High flow rates are maintained (up to 5000 cc/min.) at a constant rate without bubbles . . . During perfusion period entire extra-corporeal system is balanced by merely regulating one pump . . . Apparatus is mobile and requires only one attendant. Request information on the new Mayo-Gibbon Lung.



MARK-CLOWES HEART-LUNG Protects blood from direct exposure to gas by diffusing oxygen and carbon dioxide through thin plastic membranes. This "closed system" offers the advantages of a fixed fluid volume and a positive return of blood without danger of entraining bubbles of gas during perfusion . . . Provides flow rates of 80 cc/min. or more per kilog. of patient's weight . . . Surface area can oxygenate blood of adult man . . . Blood contacts Tygon and Teflon plastic — both atraumatic . . . Apparatus is mobile, automatic, requires only one attendant.



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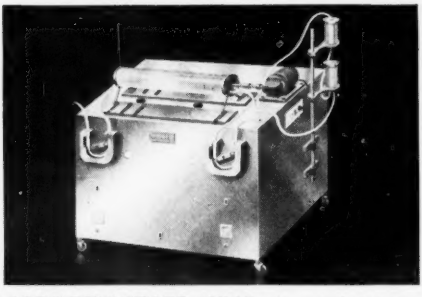

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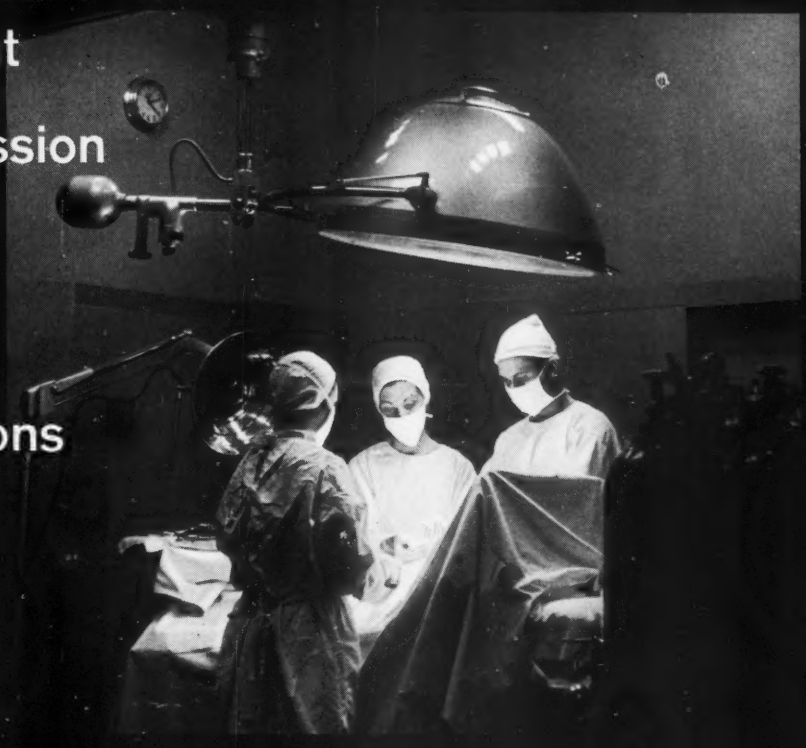

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1. Pulaski, E. J., and Isokane, R. K.: Surg., Gynec. & Obst., 104:310, March 1957.
2. Petersdorf, R. G., Curtin, J. A., and Bennett, I. L.: Arch. Int. Med. 100:927, December 1957.

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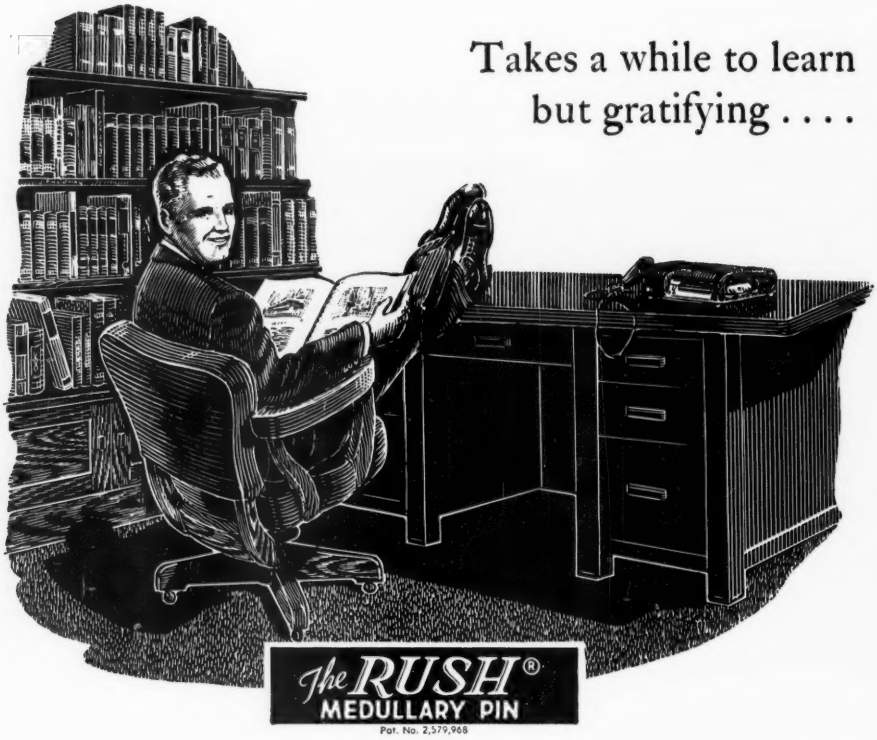

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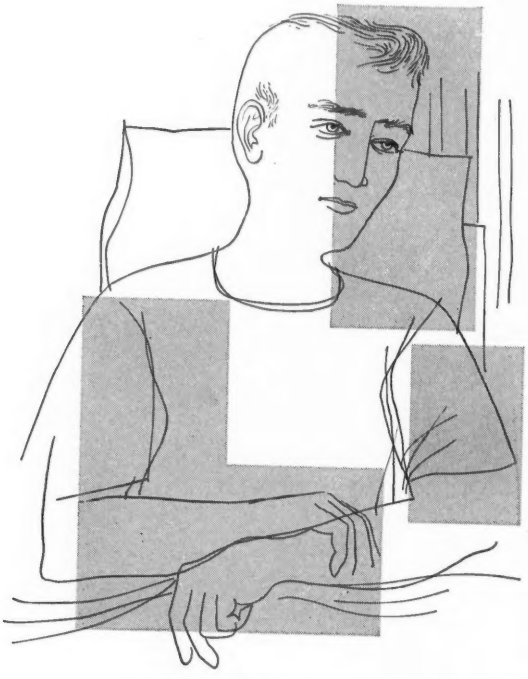

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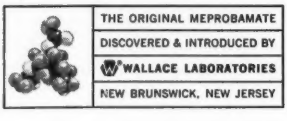

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1. *Rushia, E. L.: Preliminary report on the use of meprobamate for pre-anesthetic sedation. J.M.A. Georgia* **46**:*93, March 1957.*
2. *Lamphier, T. A.: The role of meprobamate in postoperative surgical care. Ann. New York Acad. Sc.* **67**:*810, May 9, 1957.*
3. *Kern, E. C.: Preoperative sedation with meprobamate (Miltown) in surgery of eye, ear, nose and throat. Eye, Ear, Nose & Throat Month.* **36**: *408, July 1957.*

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*Rock, J.; Pincus, G., & Garcia, C. R.: *Science* 124:891 (Nov. 2) 1956.

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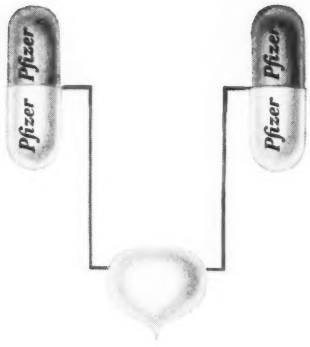

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REFERENCES: Bourque, J. P., and **Joyal, J.:** A Clinical Study of a New Sulfonamide in the Treatment of Urinary Infections, Canad. M. A. J. **68**:337, 1953. **Trafton, H. M.,** and **Lind, H. E.:** Urinary Infections, Clinical and Bacteriological Cure with Terramycin, J. Urol. **69**:315, 1953. **Musselman, M. M.:** Terramycin, Antibiotics Monographs No. 6, New York, Medical Encyclopedia, Inc., 1956. **Longley, J. R.:** Oxytetracycline Therapy in Surgery and Infections of the Urinary Tract, Antibiotics Annual 1955-1956, New York, Medical Encyclopedia, Inc., 1956, p. 358.

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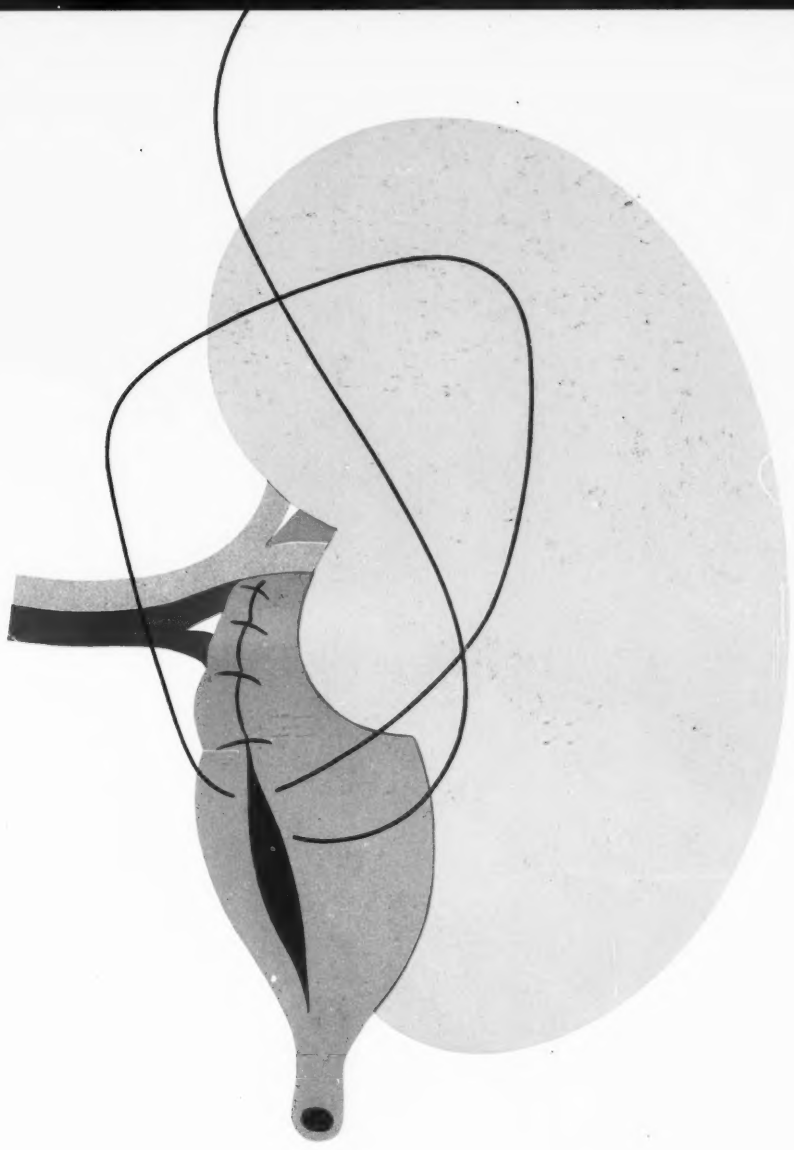

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1. Grayzel, H. G., and Schapiro, S.: Western J. Surgery, Obstet. & Gyn., Oct. 1956.

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1. Rogers, S. F., and Moore, J.: Texas J. M. 53:338, 1957. 2. Schwartz, J.: Am. J. Obst. 63:579, 1952.

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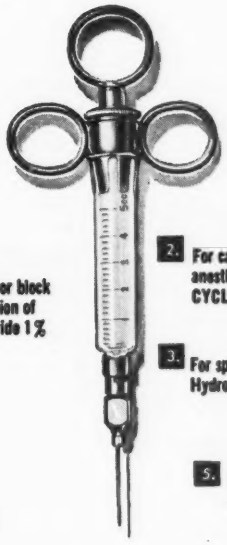

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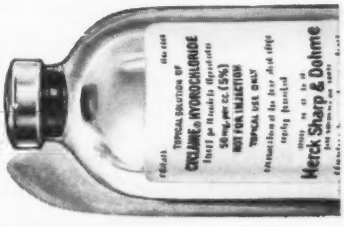

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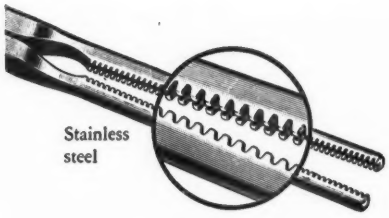

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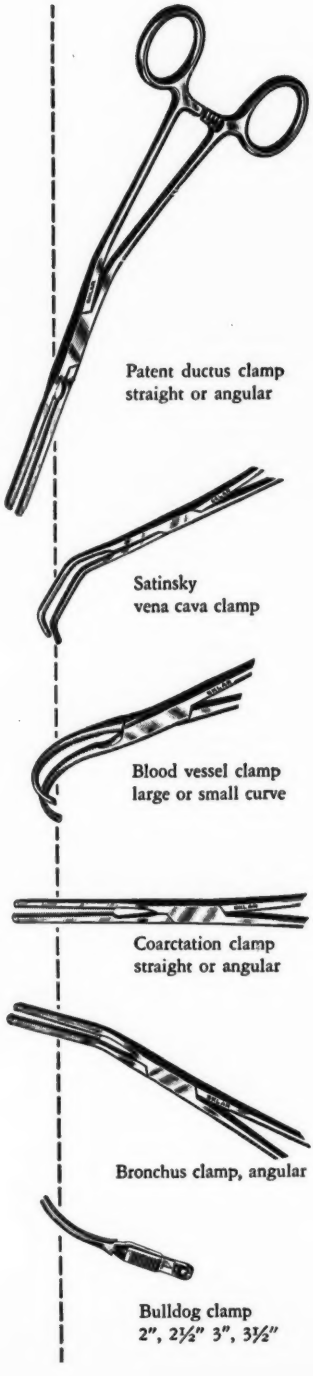

Patent ductus clamp
straight or angular

Satinsky
vena cava clamp

Blood vessel clamp
large or small curve

Coarctation clamp
straight or angular

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Bulldog clamp
2", 2½" 3", 3½"

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Squibb Triflupromazine

PROMPT, POTENT and LONG-LASTING ANTIEMETIC ACTIVITY

Clinical investigators report that in clinical studies*

Post-operatively	After Nitrogen Mustard Therapy	In Chronic Nausea and Vomiting	In Infections, Intra-abdominal Disease, and Carcinomatosis	In Neurosurgical Diagnostic Procedures	In Pregnancy When Vomiting is Persistent

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- showed potent antiemetic action
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- often markedly depressed or abolished the gag reflex
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*Reports to the Squibb Institute for Medical Research

antiemetic dosage: *Intravenous route*—8 mg. average single dose; dosage range 5 to 10 mg.
Intramuscular route—15 mg. average single dose; dosage range 5 to 15 mg.
Oral route—10 to 20 mg. initially, subsequently 10 mg. t.i.d.

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Oral Tablets—10 mg., 25 mg., 50 mg., in bottles of 50 and 500

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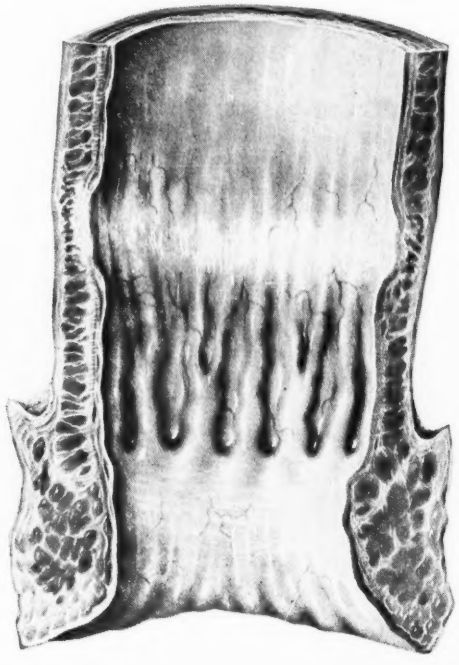

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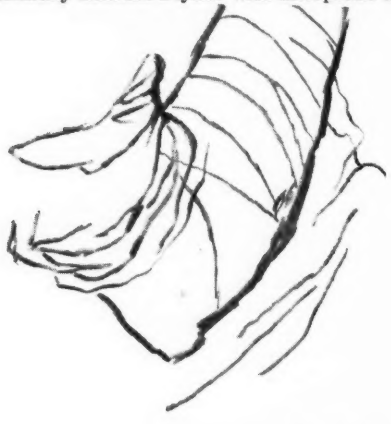

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Thiamine Mononitrate	10 mg.
Riboflavin	10 mg.
Pyridoxine Hydrochloride	2 mg.
Niacinamide	100 mg.
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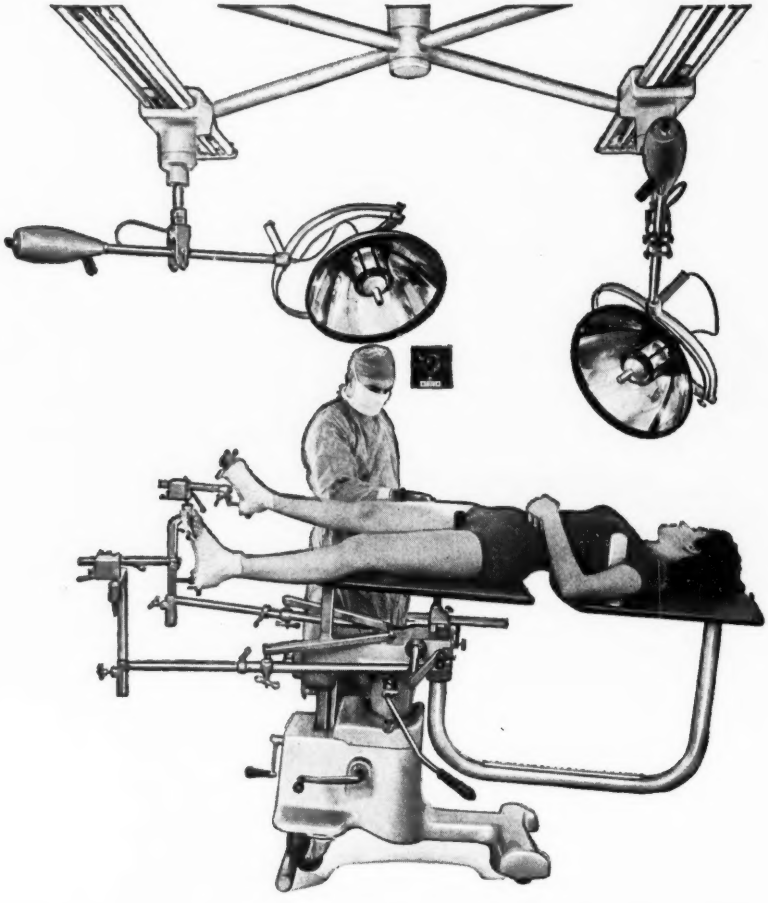

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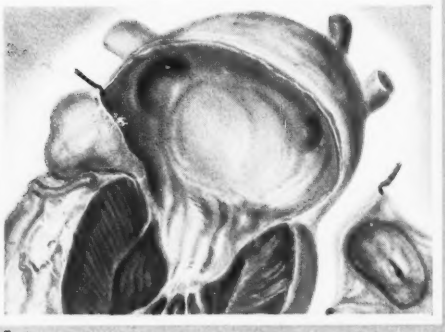
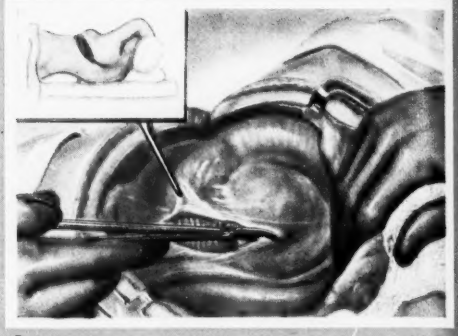
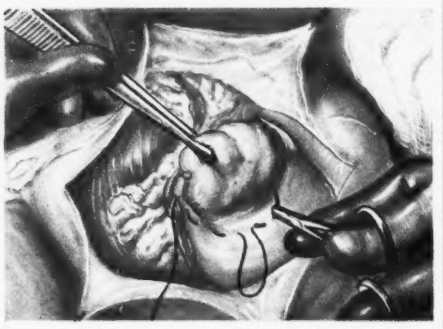
KEY ADVANCES IN OPERATIVE TECHNICS*—*Mitral Commissurotomy*[1]



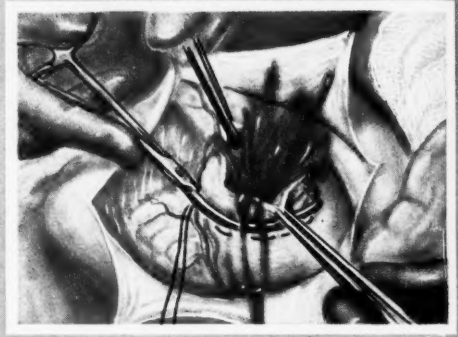
1. Interior postero-lateral view of heart. Note greatly dilated left auricle and calcified, thickened mitral valve. Inset shows typical narrowing of valve viewed from above.



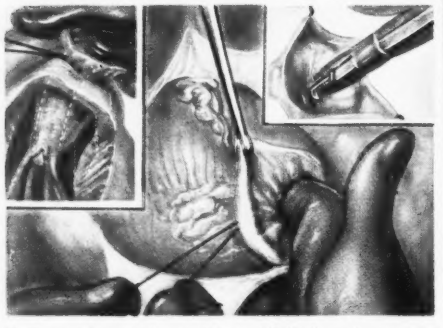
2. Postero-lateral periscapular incision. Enlargement of left ventricle and pulmonary artery is evident. Dilated left auricle presses on esophagus. Pericardium is being incised just posterior to the phrenic nerve.



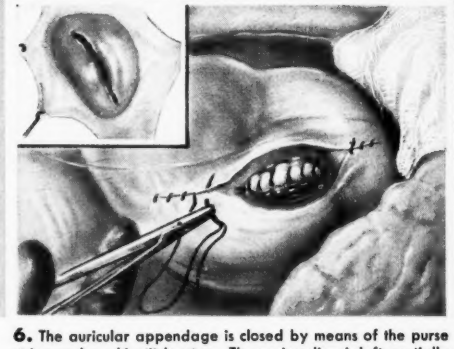
3. A purse string suture is placed around the auricular appendage. This suture is carefully started just above the circumflex artery.



4. A clamp placed just above the suture line is released slightly allowing a gush of blood to wash away any accumulated thrombotic material. Purse string suture is then tightened.



5. Finger is inserted into auricle. Inset (left) shows finger about to dilate valve. Inset (right) depicts alternate procedure with guillotine knife fastened to finger for rigid valve.



6. The auricular appendage is closed by means of the purse string and a whipstitch suture. The pericardium is left partially open. Inset shows an adequate commissurotomy.

Mitral commissurotomy is one of a series of surgical drawings in color illustrating important new operations successfully perfected during the past decade. It is brought to you as a service by Seamless, the world's largest manufacturer of surgeons' gloves. If you would care to examine any of the Seamless Gloves . . . Brown Milled, White or Brown 'Limber-Latex', or the new 'Crest' for eye, brain or heart surgery, write for a sample giving your glove size.

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1. Glover, R.P., *International Symposium on Cardiovascular Surgery*, Edited by Conrad R. Lam, (Philadelphia: W. B. Saunders Company, 1955), pp. 179-211.

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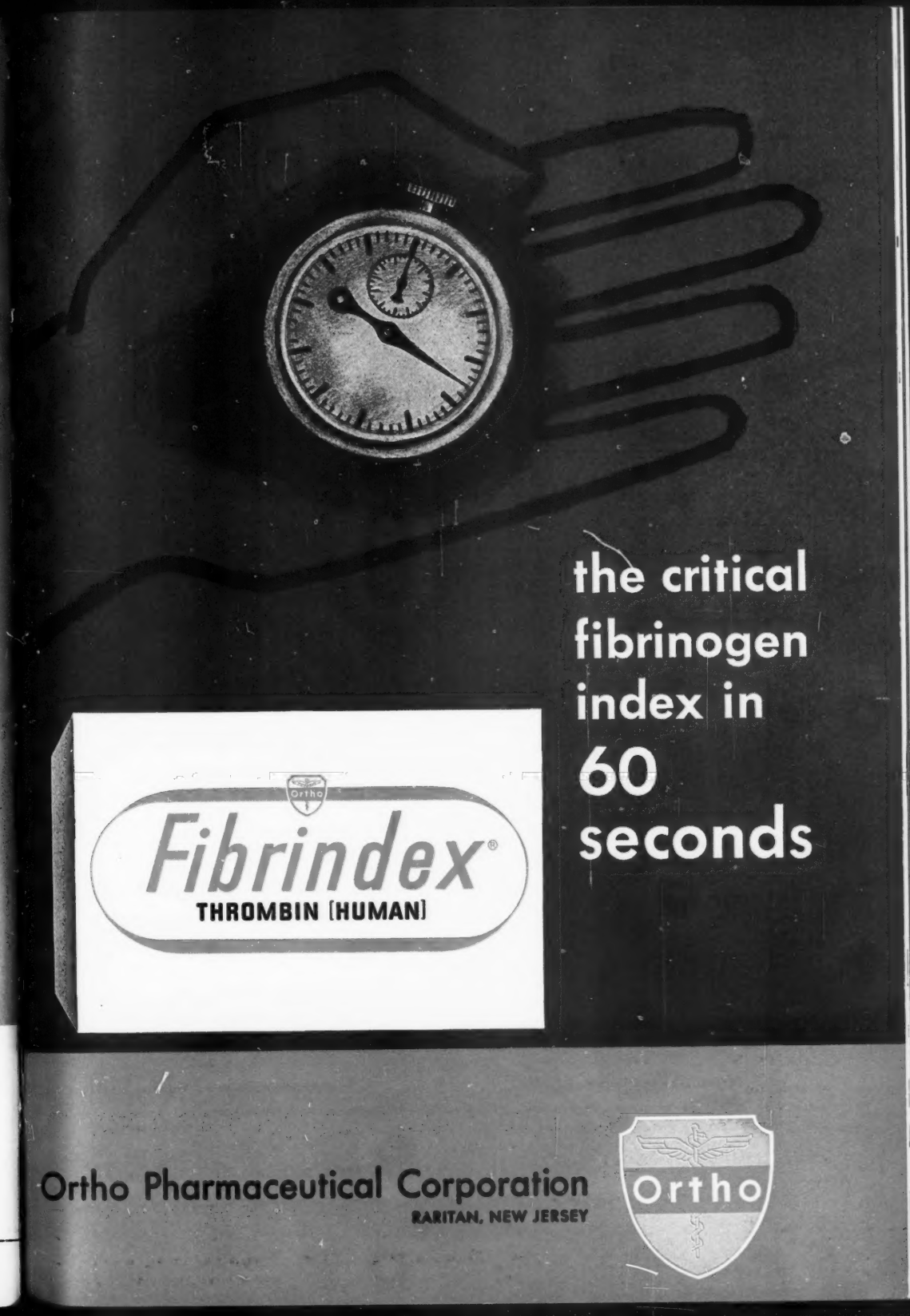
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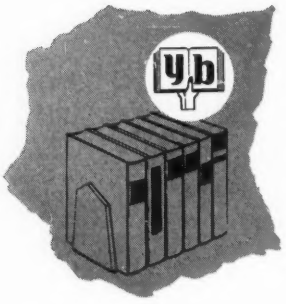

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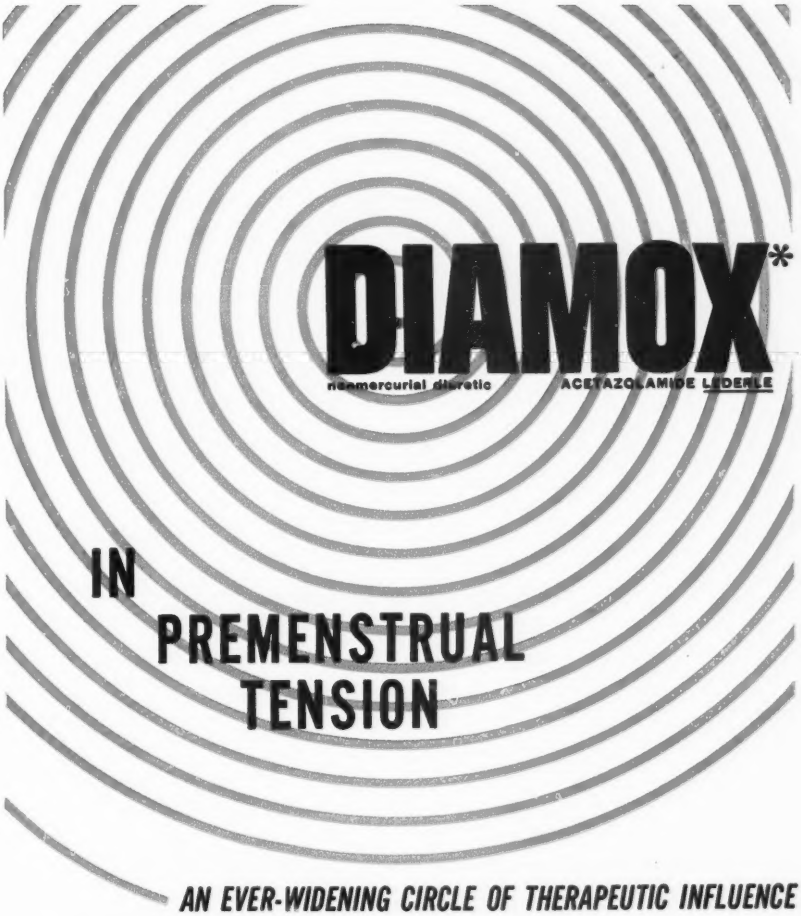

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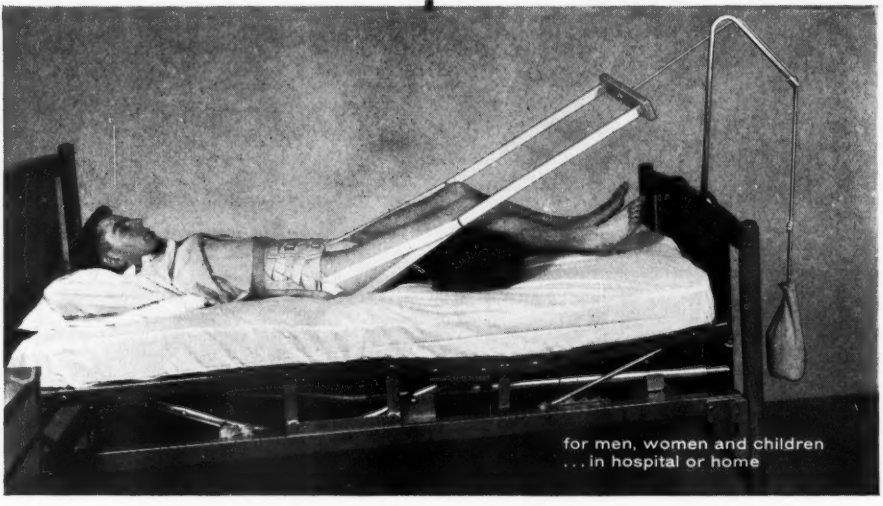

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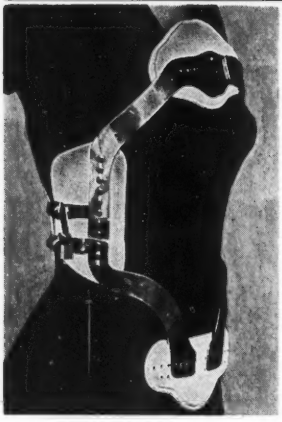

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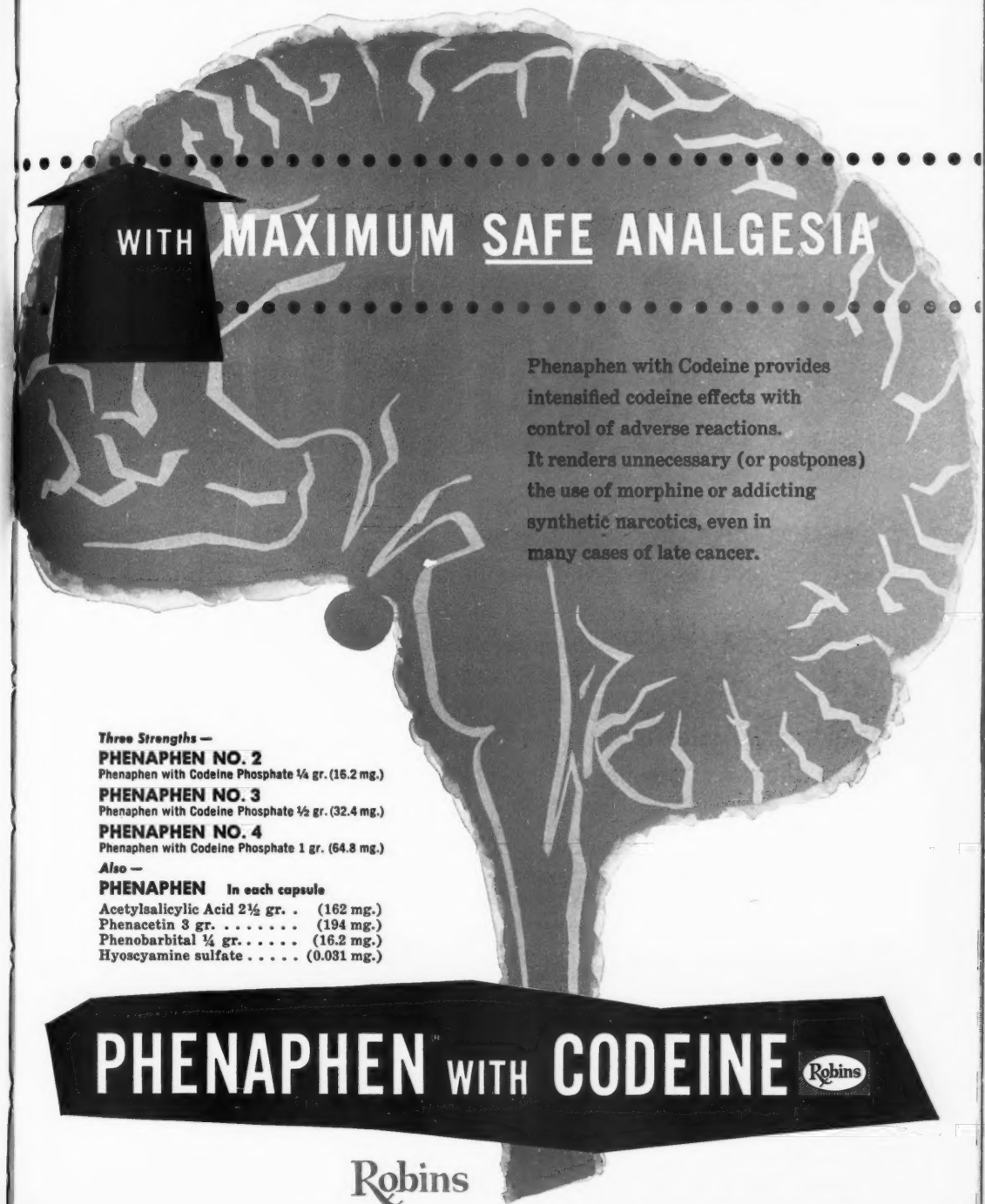

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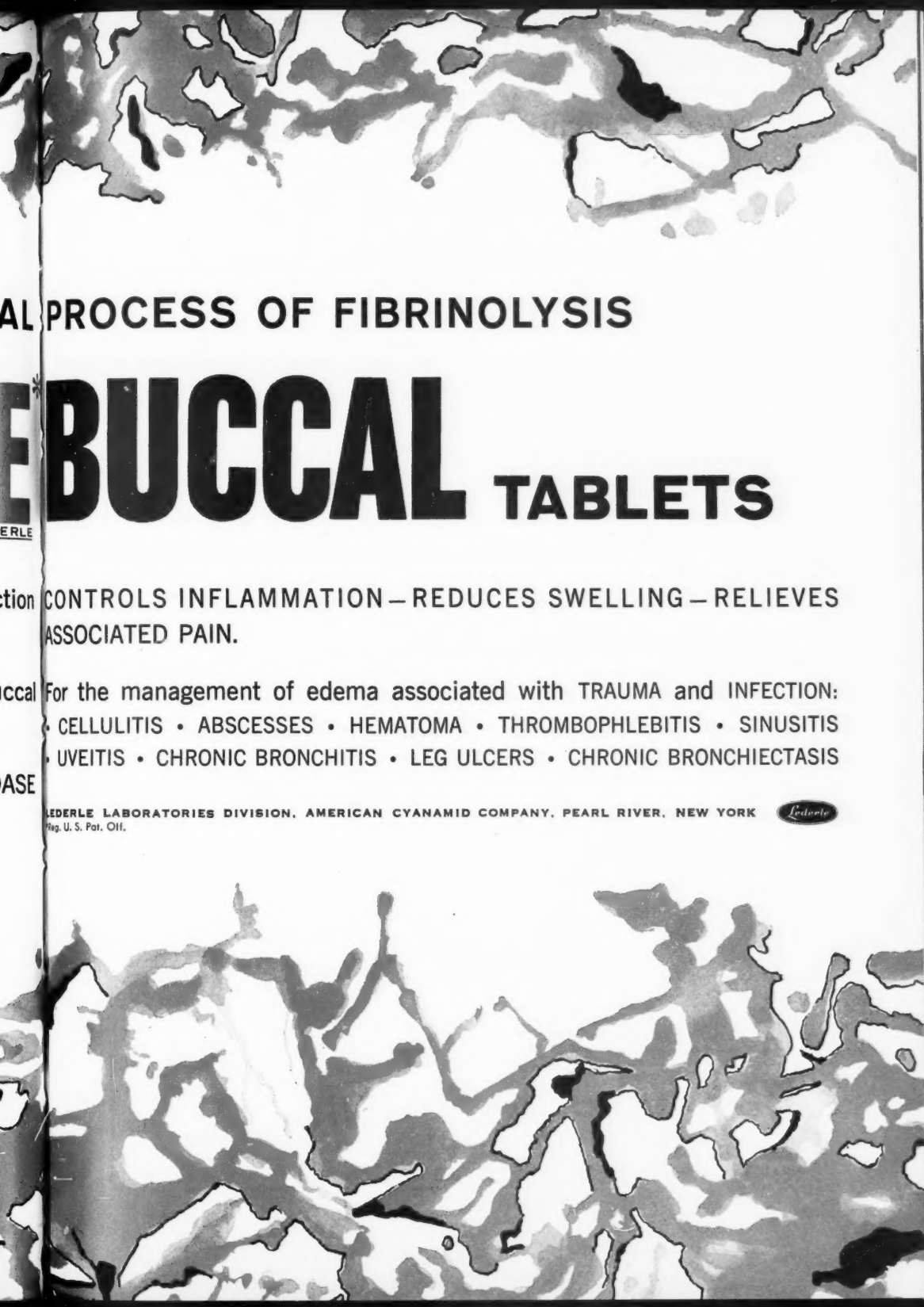
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CONTROLS INFLAMMATION—REDUCES SWELLING—RELIEVES ASSOCIATED PAIN.
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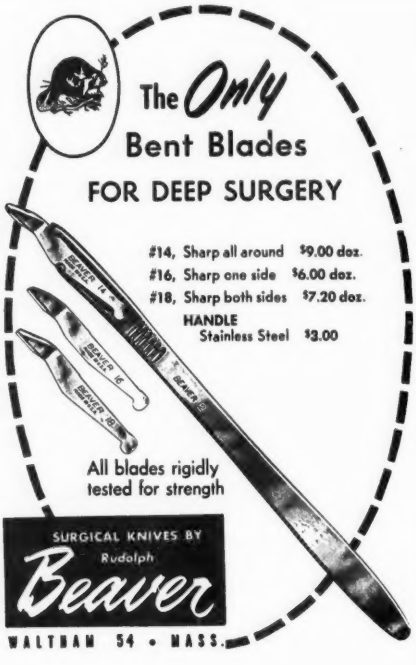

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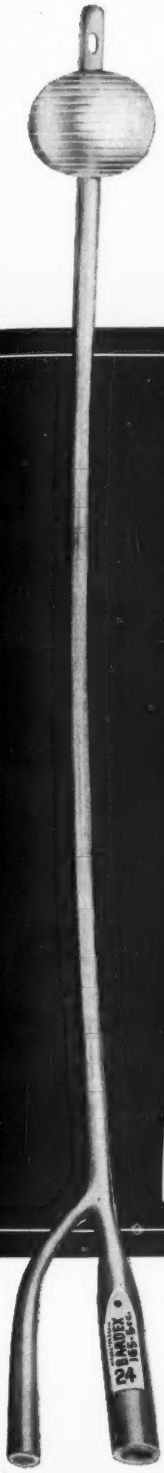

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EYE	Properly placed and sized in strong, reinforced tip. Design that assures entirely proper drainage.
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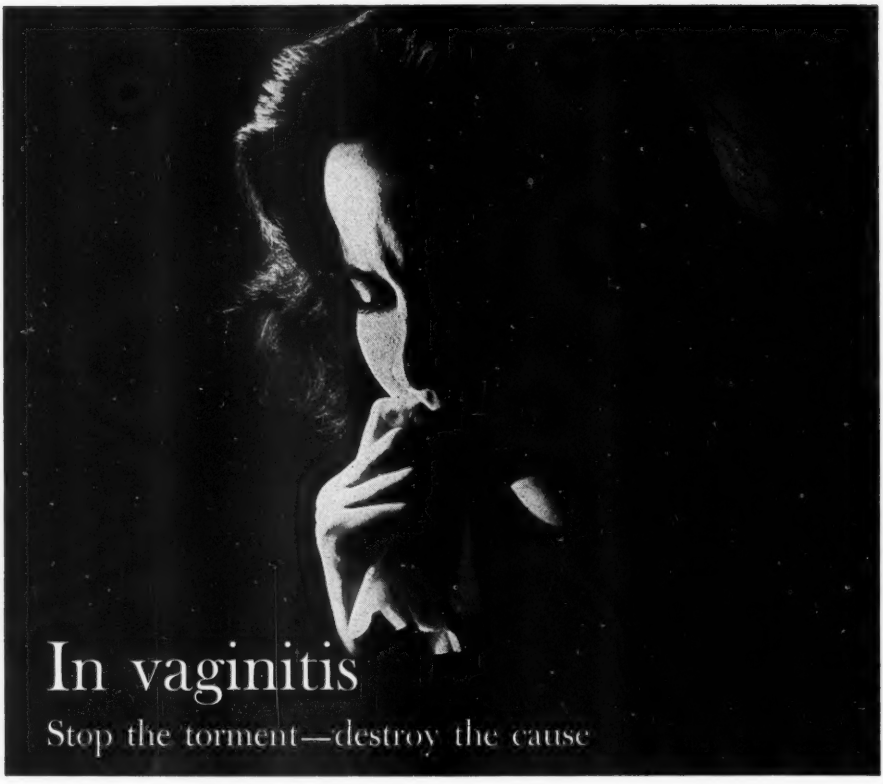

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in trichomonal vaginitis –
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in monilial vaginitis –
"... more effective than any other agent ... used previously."[2]

in mixed infection –
"... the most effective treatment of endocervicitis. ..."[3]

The rate of cure with AVC Improved is consistently high in all common types of vaginitis. In one series of patients with trichomonal vaginitis, bacteriologic cures were obtained in 82.5% of the cases.[1] Symptomatic relief is rapid and lasting. And because AVC Improved has an acid pH, it encourages the early return of normal vaginal flora.

Composition: A nonstaining cream containing 9-aminoacridine hydrochloride 0.2%; sulfanilamide 15.0%; allantoin 2.0%; with lactose in a water-miscible base buffered to pH 4.5.

Indications: Trichomonal leukorrhea; monilial and nonspecific vaginitis; cervicitis; postpartum hygiene; pre- and postcauterization, coagulation, conization, and other vaginal surgery; vaginal infections in children.

Administration: An applicatorful twice daily—on arising and at bedtime.

Supplied: 4 oz. tubes with or without applicator.

(1) Cortese, J. T.: Clin. Med. *2*:45, 1955. (2) Hensel, H. A.: Postgrad. Med. *8*:293, 1950. (3) Horoschak, A. and Horoschak, S.: J. M. Soc. New Jersey *43*:92, 1946.

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Reduce the hazard of hemorrhage due to hypoprothrombinemia during or after surgery: tonsillectomy, obstetrical and gynecological procedures, surgery of the newborn (especially prematures), neurosurgery, thoracic surgery, intestinal surgery, biliary tract surgery, rhinoplasty, surgery in any highly vascular area.

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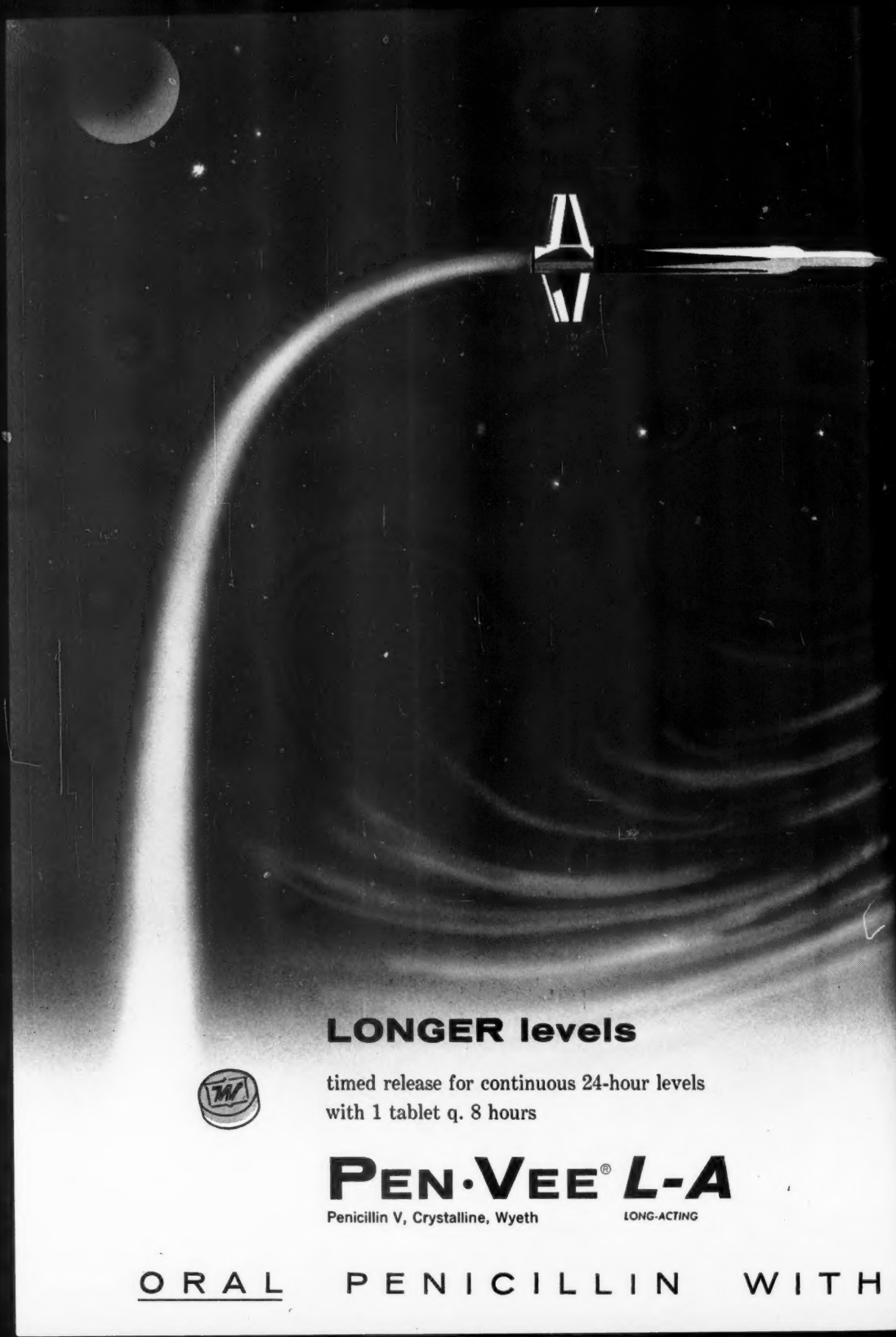
*Council on Pharmacy and Chemistry: New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Co., 1956, p. 505.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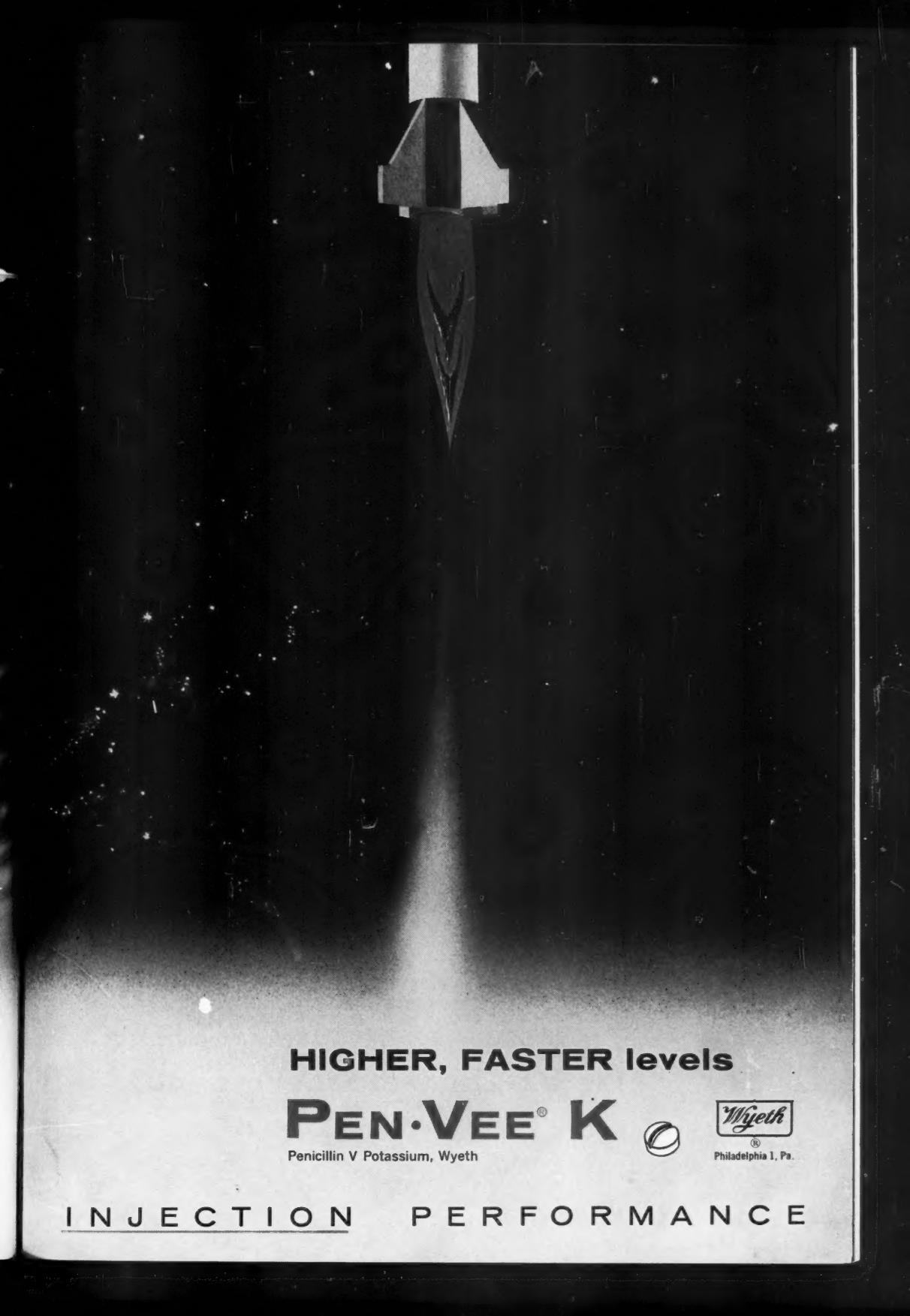
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With even the most rapid antibacterial action, pain of urinary tract infection usually persists until healing begins. So Azo Gantrisin adds *symptomatic* relief to potent antibacterial action: its azo component offers swift suppression of both pain and discomfort during this interim phase.

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simple as 1 2 3

especially for urinary tract infections

1 indications:

Urinary tract infections when associated with pain or discomfort. Particularly useful in cystitis, prostatitis and urethritis when due to susceptible organisms. Also valuable before and after urologic surgery, cystoscopy and catheterization.

2 description:

Azo Gantrisin provides — in a single tablet — the wide-spectrum, well-tolerated antibacterial action of Gantrisin, the highly soluble, single sulfonamide, together with the local analgesic action of phenylazo-diamino-pyridine HCl.

3 properties:

Not only does Gantrisin provide high urinary concentrations with little likelihood of renal blocking, but therapeutic blood and lymph levels can be readily achieved and maintained. This is significant in view of the fact that the majority of urinary tract infections are carried to the kidney by the blood stream. Phenylazo-diamino-pyridine HCl is a local analgesic agent useful in urinary tract disorders; it generally provides rapid relief of dysuria, burning and frequency. The orange-red dye appears promptly in the urine; this often has a favorable psychologic effect.

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(1) Noojin, R. O.: South. M. J. *49*:149, *162*:1379, 1956. (3) Goldman, L.; Flatt, *25*:75, 1955. (4) Frank, L., and Stritzler, (5) Robinson, R. C. V., and Robinson, (6) Canizares, O.; Shatin, H., and Rosen 1955.

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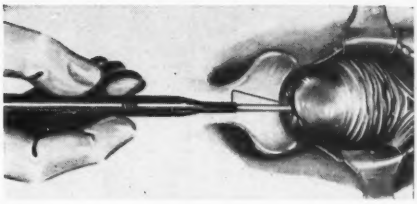

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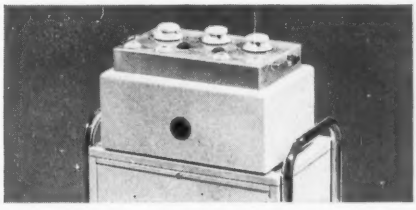

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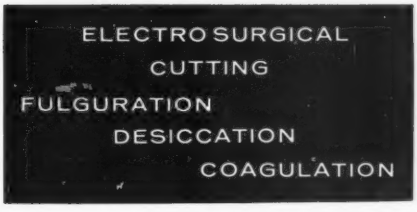

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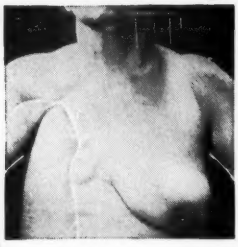

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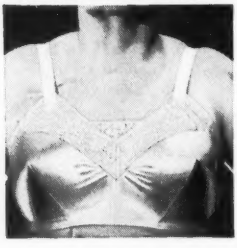

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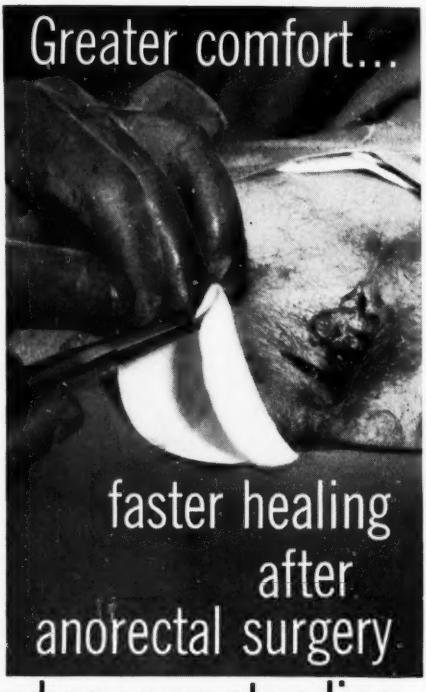

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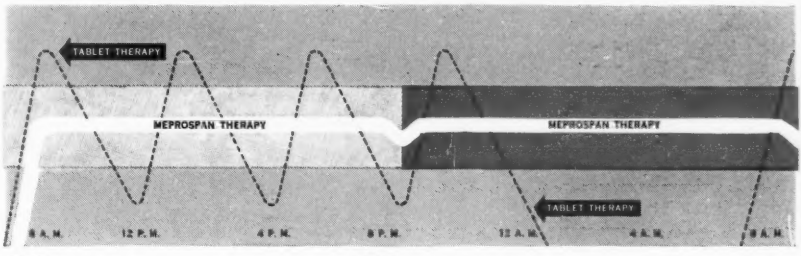

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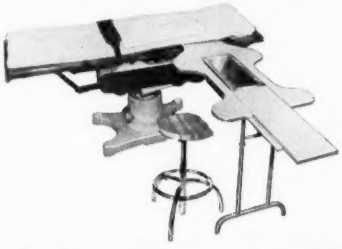

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SUPPLIED:

CAPSULES contain 250 mg. tetracycline HCl equivalent (phosphate-buffered) and 250,000 units Nystatin. ORAL SUSPENSION (cherry-mint flavored) Each 5 cc. teaspoonful contains 125 mg. tetracycline HCl equivalent (phosphate-buffered) and 125,000 units Nystatin.

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ACHROSTATIN V combines ACHROMYCIN† V . . . the new rapid-acting oral form of ACHROMYCIN† Tetracycline . . . noted for its outstanding effectiveness against more than 50 different infections . . . and NYSTATIN . . . the antifungal specific. ACHROSTATIN V provides particularly effective therapy for those patients prone to monilial overgrowth during a protracted course of antibiotic treatment.

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premenstrual

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(CHLOROTHIAZIDE)

FORD, R. V., Rochelle, J.B.III, Handley, C. A., Moyer, J. H. and Spurr, C. L.: J.A.M.A. **166**:129, Jan. 11, 1958.

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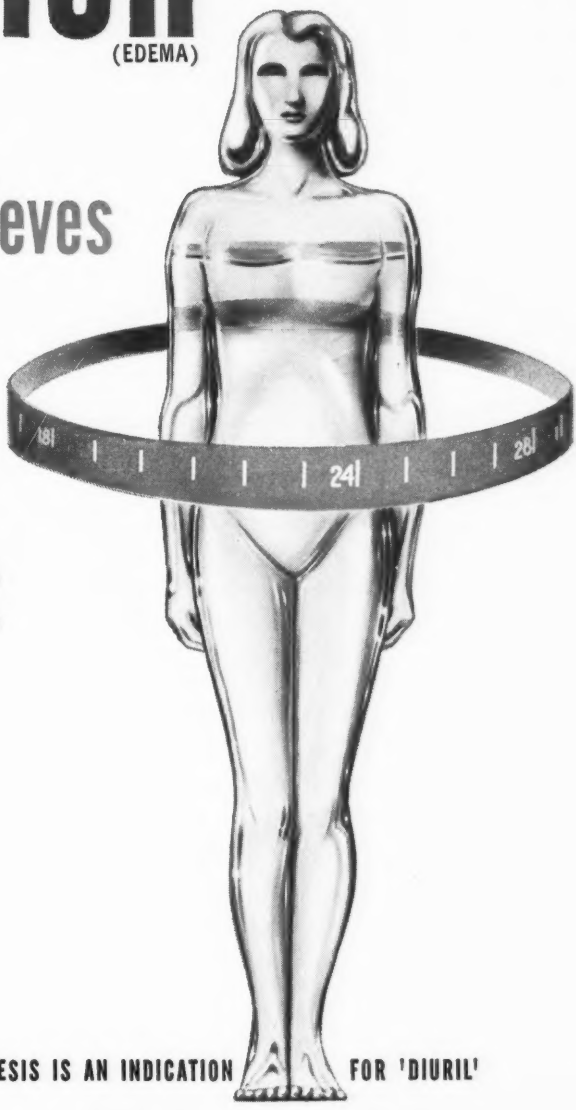
Discomfort



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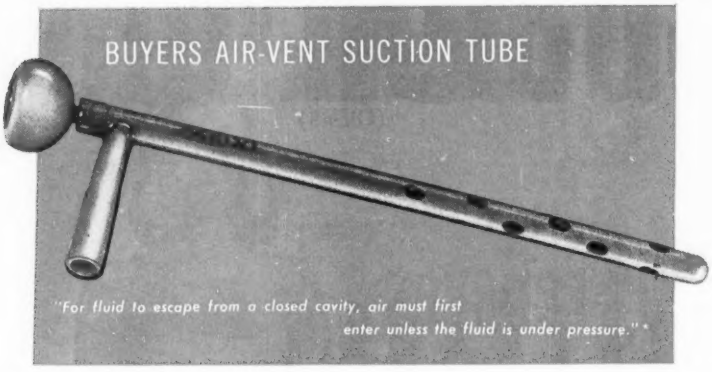
Superior New Drain
For Abdominal And Other Body Cavities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"For fluid to escape from a closed cavity, air must first enter unless the fluid is under pressure."*

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- As suction is applied, air enters the cavity through the internal catheter, mixes with the exudate and provides a very satisfactory, relatively rapid drainage.
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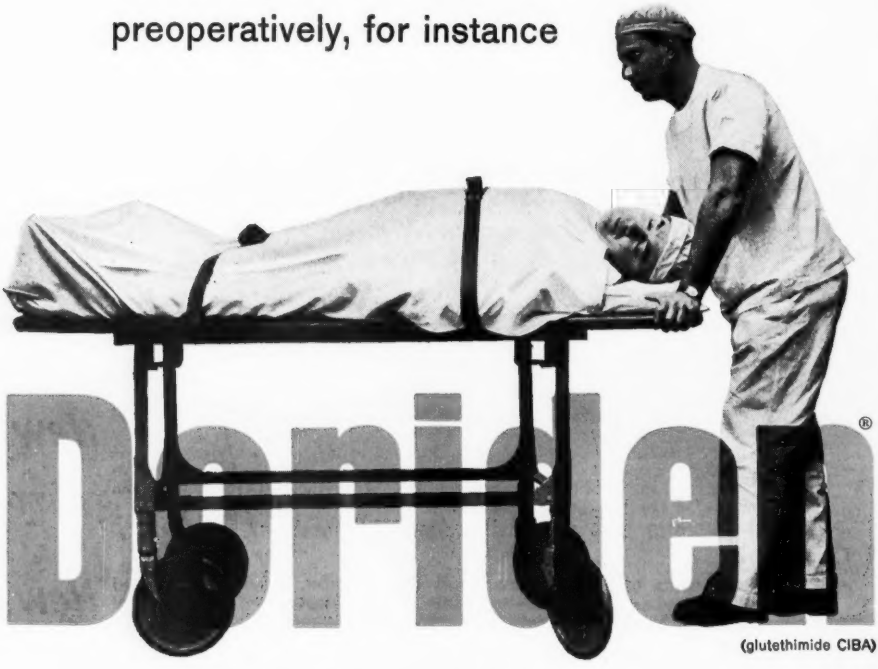

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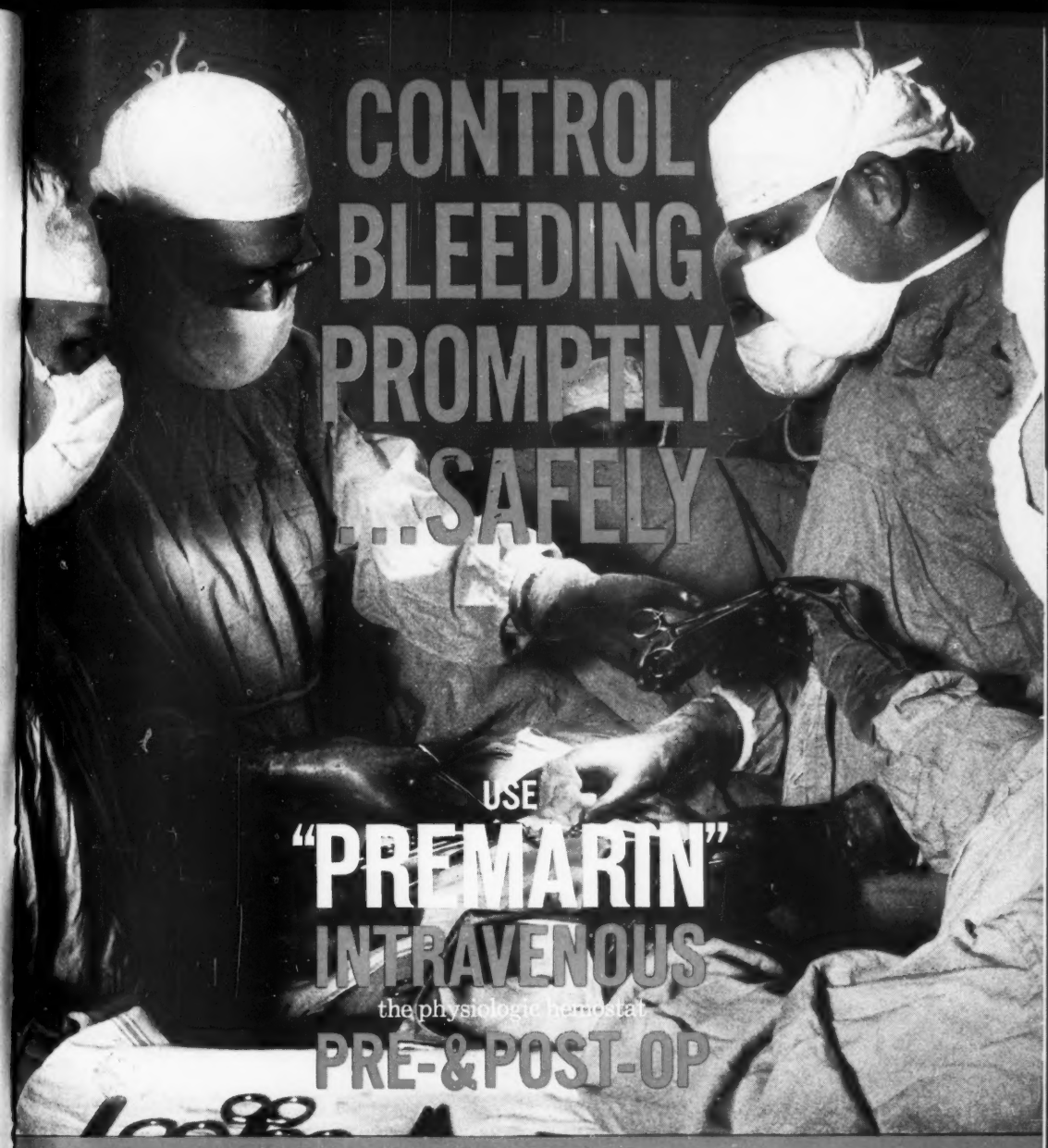

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AMERICAN CYANAMID COMPANY, LEDERLE LABORATORIES DIVISION. 28, 39, 50, 99, 104–105, 119
AMERICAN CYANAMID COMPANY, SURGICAL PRODUCTS DIVISION. .....2nd Cover, 21
AMERICAN CYSTOSCOPE MAKERS, INC. 29
AMERICAN EXPRESS COMPANY 102
AMERICAN HOSPITAL SUPPLY CORPORATION ... 6
AMERICAN MEAT INSTITUTE. 10
AMERICAN STERILIZER COMPANY. 96
APPLETON-CENTURY-CROFTS, INC. 42
AYERST LABORATORIES. 27, 125
C. R. BARD, INC. 107
BARD-PARKER COMPANY, INC. 26
BAUER & BLACK. 22
BAXTER-TRAVENOL LABORATORIES. 6
RUDOLPH BEAVER. 106
JULIUS BERBECKER & SONS, INC. 126
THE BERIVON COMPANY. 74
THE BIRTCHER CORPORATION. 115
BRISTOL LABORATORIES, INC. 62–63, 72–73
BURROUGHS WELLCOME & CO., INC. 59
S. H. CAMP & COMPANY 100
CHESEBROUGH-POND'S, INC. 43
CIBA PHARMACEUTICAL PRODUCTS, INC. 64, 124
CODMAN & SHURTLEFF, INC. 118
CUTTER LABORATORIES. 8
DAVOL RUBBER COMPANY 122
J. A. DEKNATEL AND SONS INC. 18
DESITIN CHEMICAL CORP. 81
DOME CHEMICALS INC. 75
DUKE LABORATORIES, INC. 126
EASTMAN KODAK COMPANY
Insert between 48 & 49
EATON LABORATORIES. 36–37, 83
ETHICON, INC. .....4, Insert between 80 & 81
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E. FOUGERA & COMPANY, INC. 47
FULLER PHARMACEUTICAL COMPANY 116
HYLAND LABORATORIES. 67
IDENTICAL FORM, INC. 116
LAKESIDE LABORATORIES, INC. 48
THE LIEBEL-FLARSHEIM COMPANY 46
ELI LILLY AND COMPANY. 86
MALTBIE LABORATORIES DIVISION, WALLACE & TIERNAN, INC. .....Insert between 16 & 17
THE MARK COMPANY. 68
MEAD JOHNSON & COMPANY. 16
THE MEDICAL PROTECTIVE COMPANY. 118
MERCK SHARP & DOHME. . .1, 34, 40–41, 55, 70, 89, 101, 106, 109, 120–121
V. MUELLER & COMPANY. 95
THE NATIONAL DRUG COMPANY. 108
OHIO CHEMICAL & SURGICAL EQUIPMENT CO. . 85
ORGANON, INC. 84
ORTHO PHARMACEUTICAL CORPORATION. ...11, 97
PARKE, DAVIS & COMPANY 19, 78–79
PFIZER LABORATORIES. 32, 49, 80
PHARMASEAL LABORATORIES. 51
GEORGE P. PILLING & SON CO. 38
THE PIONEER RUBBER COMPANY 60
THE QUAKER OATS COMPANY. 58
RICHARDS MANUFACTURING COMPANY. 118
RIKER LABORATORIES, INC. 24–25
A. H. ROBINS COMPANY, INC. 61, 103
ROCHE LABORATORIES, DIVISION OF HOFFMANN-LAROCHE, INC.
54, Insert between 112 & 113
J. B. ROERIG AND COMPANY. 44–45
SANBORN COMPANY 53
SCHERING CORPORATION 12–13, 113
THE SEAMLESS RUBBER COMPANY
Insert between 96 & 97
G. D. SEARLE & COMPANY 2
SHAMPAINE COMPANY. 56–57
J. SKLAR MANUFACTURING COMPANY. 90
SMITH, KLINE & FRENCH LABORATORIES
77, 4th Cover
E. R. SQUIBB & SONS. 35, 91
THERM-O-RITE PRODUCTS CO. 15
CHARLES C THOMAS PUBLISHER. 123
WALLACE LABORATORIES. 14, 23, 52, 76, 117
WARNER-CHILCOTT LABORATORIES DIV. 82, 93
THE WARREN-TEED PRODUCTS COMPANY 112
EDWARD WECK & CO., INC. 87
WESTWOOD PHARMACEUTICALS. 33
WHITE LABORATORIES 94
WILSON RUBBER COMPANY 71
WINTHROP LABORATORIES, INC. .....65, 3rd Cover
WOODWARD MEDICAL PERSONNEL BUREAU 118
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